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Epidemiological and clinicopathological parameters related to the neoadjuvant chemotherapy for breast cancer during the COVID-19 crisis

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ABSTRACT

Introduction: Breast cancer, the second-leading cause of cancer-related deaths among women worldwide, is a complex and heterogeneous disease. Its socioeconomic aspects are recognized as determinants of clinical outcomes. The COVID-19 crisis negatively affected millions, particularly in impoverished macroregions like Brazil. Thus, influences on breast cancer patients' journey may occur, particularly in the neoadjuvant settings, in which a coordinated and multidisciplinary approach is mandatory. The present study aimed to analyze the epidemiological and clinicopathological profile of breast cancer patients who underwent neoadjuvant chemotherapy during the pandemic in Brazil. **Methods:** This is a unicentric, retrospective, and descriptive cross-sectional study conducted by analyzing data obtained from electronic medical records of breast cancer patients who underwent neoadjuvant chemotherapy. **Results:** From March 2020 to December 2022, 55 patients underwent neoadjuvant chemotherapy. They presented an average age of 50.0 years (range 43.9–47.6). About 83.6% of the tumors were invasive ductal carcinomas, and the most prevalent molecular subtype was hormone receptor-positive. T2 tumors accounted for 50.9%, while compromised N1 axillary lymph nodes represented 52.7%. The most commonly used neoadjuvant chemotherapy combined anthracyclines, cyclophosphamide, and sequential taxane. Regarding postoperative pathological response, 42.2% showed a partial response after neoadjuvant treatment, and a complete pathological response of as high as 40.0% occurred. The luminal and hybrid luminal subtypes were those that achieved the greatest response to neoadjuvant therapy. The lack of pathological response was only found in the luminal molecular subtype. **Conclusions:** This study demonstrated the impacts of the COVID-19 pandemic on breast cancer patients' journey. During this period of disruption in healthcare assistance, the disease presented at more advanced stages, but the pathologic complete response was higher than expected, and influences on chemotherapy decisions were not relevant. Overall, there were efforts to keep patients in the best breast cancer care.

KEYWORDS: breast neoplasms; breast; neoadjuvant therapy; COVID-19.

INTRODUCTION

Breast cancer, the second-leading cause of cancer-related deaths among women worldwide, is a major public health issue. Considering the complexity of this malignancy, socioeconomic inequalities may impact its relevant clinical outcomes. During the COVID-19 pandemic, whose beginning was recognized by the World Health Organization on March 20, 2020, approximately 90% of countries experienced setbacks in healthcare services, particularly in elective outpatient care, routine examinations, and complementary propaedeutics, focusing on emergency care[1]. It was even more evident in the most vulnerable populations, which includes Brazil, a continental developing country[2].

As a result of delays in the cancer patients' journey, from screening to treatment, it was reported an increase in the diagnosis of breast cancer in locally advanced stages, which requires multimodal therapies, notably the combination of neoadjuvant chemotherapy, surgery, and radiation therapy[3].

By addressing micrometastases early, neoadjuvant chemotherapy aims to downstage the tumor to enable conservative surgery, evaluate *in vivo* response to systemic therapy, obtain

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prognostic information, reduce the need for axillary dissection in cases of clinically positive axilla at the initial diagnosis, and provide time for surgical planning and genetic counseling[4]. Randomized prospective studies have shown the benefits of neoadjuvant systemic therapy compared to adjuvant therapy in operable tumors (T1–T3, N0–N1, M0), but with no differences in overall survival.

In the decision-making process involved in breast cancer, phenotypic subtype, histopathological aspects, and epidemiological data such as age and menopausal status should be considered. As these data might have changed significantly during the pandemic, this study analyzes clinical, epidemiological, and histopathological aspects of breast cancer patients treated with neoadjuvant chemotherapy in the COVID-19 pandemic period in Brazil.

METHODS

Patients undergoing neoadjuvant chemotherapy for breast cancer treatment at Mater Dei Hospital, a private referral center in Belo Horizonte, Brazil, between March 2020 and December 2022, were selected. Demographic and clinical data, such as age, menopausal status, family history of cancer, axillary staging, chemotherapy regimen, and pathological response to chemotherapy were gathered from electronic medical records. Histopathological data were obtained, including information on histology subtype, histological grade, tumor size, expression of hormonal receptors, human epidermal growth factor receptor-type 2 (HER2) status, Ki67 protein, molecular subtype, and degree of histological response to neoadjuvant treatment. No pathological review was performed for this analysis.

Inclusion criteria were female gender, age 18 and above, histologically confirmed diagnosis of breast cancer, multifocal disease, availability of data in electronic medical records, and neoadjuvant chemotherapy. Synchronic carcinomas were excluded, according to Figure 1.

Descriptive statistics were used to summarize the data. Normality tests (Shapiro-Wilk) were performed for each continuous variable. Categorical variables were presented as numbers and percentages, and continuous variables as medians and interquartile ranges. Statistical analysis was conducted using Statistical Package for Social Sciences - SPSS® software, version 20 (SPSS, Chicago, IL).

The study was approved by an independent Ethics Committee (CAAE 73246223.8.0000.5128), and the protocols followed the 1975 Helsinki Declaration ethical guidelines. Due to the retrospective nature of this study, the local Human Subjects Committee approved the waiver of participants' free and informed consent.

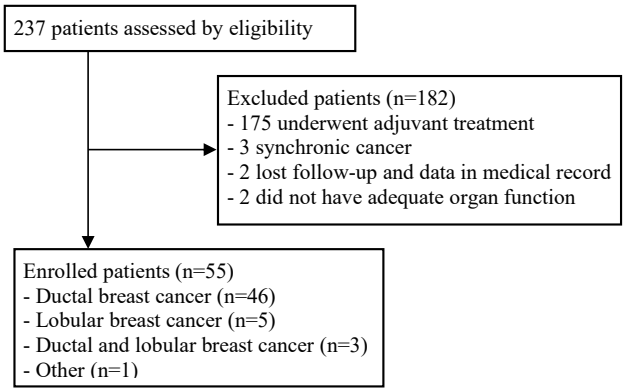

Figure 1. Trial profile.

RESULTS

Demographic data, clinical characteristics, and histopathological parameters of patients and their respective tumors were summarized in Table 1. Among the patients included in the study (n=237), 55 (22.0%) underwent neoadjuvant chemotherapy, with an average age of 50 years (range 43.9–47.6). Approximately 60% of these patients did not have a relevant family oncologic history, such as a history in first-degree relatives with breast, ovarian, or intestinal cancer. High penetrance gene mutations were found in two patients (TP53 and BRCA 2), and one had a variant of uncertain significance in the POLD1 gene.

Regarding histological aspects, approximately 83.6% of the tumors were invasive ductal carcinomas, and the most prevalent molecular subtype was hormone receptor-positive tumors. The luminal subtype (either A or B) comprised about 45.4% of the analyzed cases. T2 tumors (> 2 to 5 cm) accounted for 50.9%, followed by T3 tumors (larger than 5 cm) at 29.0%. Axillary involvement was found in 52.7% of patients, with mobile and fixed lymph nodes in the axilla ipsilateral to the tumor (respectively, N1 and N2), the majority classified as clinical staging II B. The most commonly used neoadjuvant regimen was a combination of anthracyclines, cyclophosphamide, and sequentially taxane (52.7%).

Partial pathological response after neoadjuvant treatment was seen in 42.2%, and complete pathological response (pCR) in 40.0%. When analyzing molecular subtypes, HER2-positive and hybrid luminal, patients had the highest complete response rates (80% and 50%, respectively), as show in Figure 2. The absence of pathological response to chemotherapy was found only in patients with the luminal molecular subtype, accounting for 20% of all analyzed luminal subtype patients.

DISCUSSION

The present study shows that, during the COVID-19 pandemic period, roughly 22.0% of all breast cancer patients underwent neoadjuvant therapy. Most (83.6%) presented as T2 or above, and clinical axillary involvement was detected in approximately 63.7%. Despite the challenges of keeping the patients at home in this period, the most used chemotherapy regimen

Table 1. Patients with analyzed outcomes, in which the information was available, expressed as absolute numbers and percentage.

Characteristic	Number (n=55)	%
Age		
<40	11	20.0
40–49	18	32.7
50–64	19	34.5
≥65	7	12.7
Family History		
Positive	22	40.0
Negative	33	60.0
Histology		
Ductal	46	83.6
Lobular	5	9.0
Ductal and Lobular	3	5.4
Others	1	1.8
Molecular Subtype		
Luminal	25	45.4
HER2	5	9.0
Triple Negative	10	18.1
Hybrid Luminal	15	27.2
Tumor Size		
T1	9	16.3
T2	28	50.9
T3	16	29.0
T4	2	3.6
Lymph Node Status		
N0	20	36.3
N1	29	52.7
N2	6	10.9
N3	0	0
Therapy		
ddAC-T	29	52.7
ddAC –THP	10	18.1
ddAC	7	12.7
AC-TC	4	7.2
THP	3	5.4
TCHP	2	3.6
Pathological Response		
Complete	22	40
Luminal	7	27.2
HER2	4	18.1
Triple Negative	3	13.6
Hybrid Luminal	8	36.3
Partial	26	47.2
Luminal	13	50
HER2	1	3.8
Triple Negative	5	19.2
Hybrid Luminal	7	29.9
Absent		9.0
Unknown		3.6

HER2: human epidermal growth factor receptor-type 2; ddAC-T: dose--dense anthracycline plus cyclophosphamide and sequential paclitaxel; ddAC-THP: dose-dense anthracycline plus cyclophosphamide and sequential paclitaxel plus double blockade of trastuzumab and pertuzumab; AC-TC: anthracycline plus cyclophosphamide and sequential paclitaxel plus carboplatin; THP: paclitaxel plus double blockade of trastuzumab and pertuzumab; TCHP: paclitaxel plus carboplatin plus double blockade of trastuzumab and pertuzumab,

was ddAC-T, instead of those that required fewer days for infusions, such as a combination of taxanes and carboplatin or cyclophosphamide. Moreover, the frequency of HER2 tumors was higher than usual, and pathological response rates (partial or complete) in this subgroup were more common than the other molecular subtypes.

Breast cancer is the leading cause of cancer-related deaths in Brazil, except in the Northern, considered a socioeconomic less favorable geographic region[5]. Many epidemiological and clinicopathologic characteristics are associated with relevant clinical outcomes of this malignancy and need to be pointed out.

First, breast cancer incidence rises with age, thus being less common among younger women. Most cases are diagnosed in women aged 50–64, consistent with the predominant age group in our study (34.54% of patients)[6].

Approximately 10–15% of breast cancers are associated with genetic alterations[7]. The Breast Cancer Association Consortium publication demonstrated an association between nine genes and breast cancer risk. Genes considered high-risk include BRCA1, BRCA2, PALB2, and TP53[8]. In our cohort, 40% had a family history of cancer in first-degree relatives, but only three had genetic mutations, two in high-risk genes (TP53 and BRCA2).

Over the last years, with a greater understanding of tumor molecular biology, breast cancer treatment has become increasingly complex, primarily guided by the subtype. A multidisciplinary approach becomes fundamental for treatment decisions for locally advanced cancer cases, defined as a tumor measuring over 2 cm (T2) and involving lymph nodes (N+). Almost 23% of patients underwent neoadjuvant therapy. Of those, 84.43% had T2, T3, or T4 tumors, and approximately 64% had clinically positive axilla. Due to screening failure or delay in searching for non-COVID-19-related medical assistance, we would expect a higher number of locally advanced tumors under neoadjuvant treatment. However, it is essential to mention the existence of different waves of COVID-19 cases[9]. This profile would probably be worse before vaccinations or when more new cases were reported. The resistance of patients and doctors to undergo chemotherapy during uncontrolled phases of the pandemic may also explain these findings.

In the past 40 years, medications and therapies have been developed to improve the quality of life and long-lasting outcomes for breast cancer patients. In this context, neoadjuvant treatment has emerged as a therapeutic strategy for surgical downstaging, *in vivo* assessment of systemic therapy response, and prognostic evaluation[10]. A study at the Memorial Sloan Kettering Cancer Center, between 2013 and 2019, revealed that of breast cancer patients with clinical stage I to III undergoing neoadjuvant chemotherapy, 75% presented a conversion from infeasible to feasible conservative surgery[11].

Subsequently, two major studies conducted in the United States in the 1990s demonstrated the non-inferiority of

neoadjuvant compared to adjuvant therapy regarding overall survival and progression-free survival. It was shown that patients achieving pCR had a better prognosis than those with residual disease[4]. The evaluation of this surrogate outcome as a reliable parameter was conducted in a meta-analysis published in 2014, correlating pCR with increased overall survival. This association became even more statistically evident in HER2+ patients, regardless of hormonal status, and triple-negative cases, confirmed in our study, where this group represents 84.4% of patients achieving pCR[12]. Another critical point to be explored is the high frequency of HER2+ patients in our cohort. Possibly, these patients were more often referred to neoadjuvant treatment due to advances in antiHER2 treatment in this scenario.

Today, the standard therapy for initial HER2+ subtype breast cancer patients is neoadjuvant therapy, comprising different chemotherapy regimens associated with trastuzumab with or without pertuzumab[13-15]. In our institution's study, 36.6% of patients were hybrid luminal or HER2+ types. Of these patients, 50% underwent neoadjuvant treatment with ddAC-THP, while the others were treated with de-escalated neoadjuvant protocols such as THP or TCHP, with 54.4% achieving pCR. Interestingly, these data point to the fact that the COVID-19 period did not interfere with medical decisions for regimens requiring fewer infusions despite the attempts to keep patients at home.

For triple-negative breast cancer (TNBC), current evidence indicates that treatments used in adjuvant therapy are also suitable for neoadjuvant settings. Based on the Anthracycline in Breast Cancer study, neoadjuvant treatment in TNBC patients is recommended for at least T1c and N+ using anthracycline and taxane-based chemotherapy[16,17]. In our study, ten patients (18.8%) had TNBC in our institution.

None of the TNBC patients received neoadjuvant immunotherapy despite the data from the KEYNOTE-522 study. Published in 2020, this phase 3 trial demonstrated that combining pembrolizumab with carboplatin and paclitaxel followed by anthracycline in stage II or III TNBC patients resulted in higher pCR rates (64.8% *vs.* 51.2%)[18]. However, pembrolizumab in this scenario

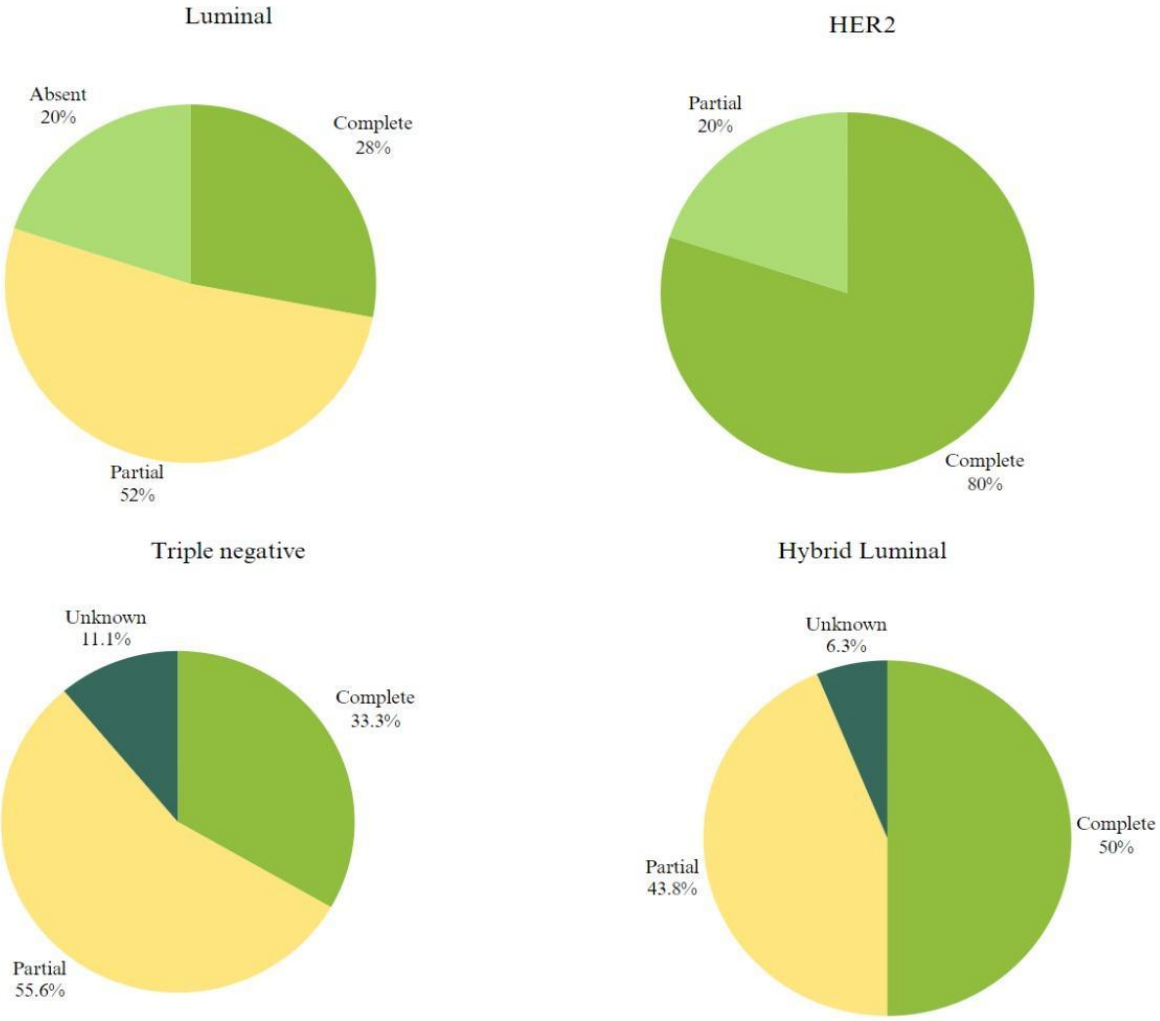

Figure 2. Analysis of pathological response according to molecular subtypes.

was only approved in May 2022 by regulatory agencies in Brazil. It needs to be clarified whether the pandemic delayed our country's approval process.

Hormone receptor-positive (HR+) and HER2- tumors, despite their high prevalence, have more restricted indications for neoadjuvant therapy compared to other histological subtypes. However, it was a useful strategy worldwide during the COVID-19 period, when temporary contraindications for surgery were required. Despite that, we expected more patients with this condition at our center. Concerns regarding virus exposition during chemotherapy may have been balanced.

It is known that neoadjuvant chemotherapy is less effective in achieving pCR in luminal tumors, especially in the luminal A subtype, compared to more aggressive histologies[19]. However, our data showed that a pCR rate of around 25% was observed, surpassing global data of around 6–11% in the literature[20]. Another intriguing finding is the absence of neoadjuvant endocrine therapy among our cohort, despite data showing pCR at least equivalent to chemotherapy ones[21].

Our study has some limitations. It was retrospective and performed in a single center, not reflecting our population's sociodemographic and genetic diversity. Moreover, information and selection bias may have occurred. However, it was an important study to assess the impact of the COVID-19 crisis among our patients, which analyzed epidemiologic and clinical pathological aspects.

CONCLUSION

The study contributed to a better understanding of the epidemiological profile of breast cancer patients who underwent neoadjuvant chemotherapy during the COVID-19 crisis when there was a disruption in healthcare assistance. Despite concerns regarding the pandemic itself, it was shown the effort to keep patients on the best assistance directed to breast cancer.

AUTHORS' CONTRIBUTION

MFMSVG: Conceptualization, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. LMACL: Data curation, Writing – original draft, Writing – review & editing. LLSC: Data curation, Formal analysis, Writing – original draft, Writhing – review & editing. MOS: Formal analysis, Investigation, Writing – review & editing. CCA: Formal analysis, Investigation. JPCA: Data curation, Validation. PHCD: Formal analysis, Investigation, Methodology, Project administration, Visualization. JTCA: Conceptualization, Methodology, Project administration, Visualization.

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Telehealth after one year of Breast Cancer Surgery as a Physical Therapy Follow-up Strategy

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ABSTRACT

Introduction: Breast cancer is the most prevalent type of invasive cancer in the female population. The surgical procedure is one of the aspects of oncological treatment. However, there are several postoperative complications resulting from this process, in which physical therapists work from prevention to treatment. During the COVID-19 pandemic, the physical therapy service implemented teleconsultations for the six-month and one-year postoperative follow-ups. The purpose of this article was to evaluate the prevalence of complications identified in physical therapy follow-up, through teleconsultation, and to describe the frequency of face-to-face evaluations to confirm the physical therapy diagnosis. **Methods:** This is a cross-sectional study, including patients submitted to surgical treatment of breast cancer, from January 2019 to September 2021, and who were seen at the one-year postoperative teleconsultation. **Results:** We included 362 patients, with a mean age of 58.17 (±12.16) years. Among the reported complications, the most frequent was paresthesia in the intercostobrachial nerve (87.1%); 23.8% of the patients reported pain; and 22.1%, phantom breast sensation. 11.9% (n=43) of the patients were referred for face-to-face evaluation, being 58.1% (n=25) due to the perception of lymphedema as the main reason for these referrals. **Conclusions:** The most frequent complications reported by patients in one-year teleconsultation were paresthesia, followed by pain and sensation of phantom breast. The greatest reason for referrals to face-to-face consultation was lymphedema. With such findings, this modality of care shows a possibility of effective follow-up in the postoperative period of breast cancer.

KEYWORDS: teleconsultation; breast cancer; physical therapy.

INTRODUCTION

According to the Brazilian National Cancer Institute (*Instituto Nacional de Câncer* – INCA), there are, for each year of the triennium 2023–2025, 73,610 thousand new estimated cases of breast cancer in Brazil, this being the most frequent type of invasive cancer in the female population[1]. The surgical procedure consists of the pillar of oncological treatment for breast cancer, and among the various complications resulting from this process are pain, sensitivity change, reduced range of motion (ROM), scar complications, sensation and pain in the phantom breast, axillary web syndrome (AWS), and lymphedema in the homolateral upper limb (HUL) in relation to surgical treatment. The physical therapist intervenes in the prevention, early detection, and treatment of these complications[2].

Researchers reinforce that the guidelines for the practice of free active movement and strengthening of the upper limbs are indispensable for kinetic-functional recovery and pain control after oncological breast surgery[3-6]. In addition, early postoperative physical therapy with exercises for the shoulder joint showed both pain reduction and improvement of ROM, and recovery of upper limb functionality for daily and labor activities[7].

Social distancing, in early 2020, was recommended due to the advance of the SARS-CoV-2 virus pandemic, in such a way it was necessary to reduce face-to-face consultations and care[8]. In order to guide healthcare professionals, the Brazilian Federal Council of Physical Therapy and Occupational Therapy (*Conselho Federal de Fisioterapia e Terapia Ocupacional* – COFFITO), through Resolution 516 of March 20, 2020, allowed the online care provided in the modalities of teleconsultation, teleconsulting, and telemonitoring by physical therapists and occupational therapists[9].

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According to Federal Law No. 14,510/2022, which authorizes the practice of telehealth throughout the Brazilian territory, telehealth consists in the provision of distance healthcare services, using communication technologies through texts, sounds, and/or images for health information, and ensures that every healthcare professional has the autonomy to decide whether or not to use telehealth whenever deemed necessary[10].

The physical therapy service of the Hospital do Câncer III [Cancer Hospital III] of the Instituto Nacional de Câncer (HC III/INCA), a hospital unit specialized in the treatment of breast cancer, has established in its routine the following physical therapeutic evaluations: first time (before starting the oncological treatment), on the first day, in 30 days, six months, and one year after surgery[11]. The physical therapy consultation of one year after breast cancer surgery is the time to evaluate the possibility of discharge of outpatient physical therapy follow-up in HC III/INCA.

In the initial period of the COVID-19 pandemic, the physical therapy service implemented the practice of telehealth, and consultations of 30 days, six months, and one year after the surgery were carried out in the form of teleconsultation. If face-to-face care was necessary, the recommendations of the Brazilian Association of Physical Therapy in Oncology (*Associação Brasileira de Fisioterapia em Oncologia* – ABFO) for prevention and biosafety against the spread of SARS-CoV-2 were followed[12]. With the control of the pandemic and the return of face-to-face care, the teleconsultation was maintained for the follow-ups of six months and one year after surgery because it allows more comfort and economy to patients[13].

In this study, our objective was to describe the prevalence of complications evaluated in physical therapy follow-up through one-year post-operative teleconsultation of breast cancer and to analyze the frequency and need for face-to-face evaluations to confirm the physical therapy diagnosis.

METHODS

This is a cross-sectional study with patients submitted to surgical treatment of breast cancer in HCIII/INCA, from January 2019 to September 2021, and who were seen via teleconsultation for evaluation and physical therapy follow-up in the one-year postoperative period.

The eligible patients were preselected through active search of the evolutions of consultations in the Care Control System of the Physical Therapy Service (*Sistema de Controle do Atendimento do Serviço de Fisioterapia* – SISCASF). Sociodemographic, clinical, and treatment data were collected from paper and electronic medical records. In addition, the following data were collected from: the physical therapeutic evolution record of the one-year postoperative teleconsultation, the postoperative complications reported, such as pain, sensation and/or pain in the phantom breast, paresthesia in the cutaneous region innervated by the intercostobrachial nerve (ICBN), intercostobrachial neuralgia (ICB), axillary web syndrome (AWS), reduced range of motion (ROM), subjective sensation of lymphedema (sensation of weight and swelling), and lymphedema (patients' perception of change in the volume of HUL).

To evaluate life habits, information regarding personal care and household chores were collected from the physical therapeutic evaluation form, classified as fully carried out, partially or not carried out, practice of home exercises with upper limbs (UL) and the frequency of these exercises, classified as regular, irregular, or not performing it, and practice of leisure physical exercises.

For certain types of complaints reported in teleconsultation, such as lymphedema in HUL, severe pain, reduced ROM, and AWS, the patient was referred to face-to-face consultation. The reason for referral to face-to-face evaluation was collected from physical therapeutic evolutions.

Of the patients referred to face-to-face evaluation, the same complications evaluated in the teleconsultation were collected, and the assessment of lymphedema was verified through perimetry of the upper limbs. Lymphedema was considered when the difference between HUL and the contralateral upper limb was ≥2.0 cm in at least one reference point.

To evaluate the perimetry of the UL, a tape measure was used and the circumference of the limb was measured at six specific points, demarcating the first point in the region of the lateral epicondyle and the others every 7-cm distance to the arm and forearm.

Descriptive analyses of measures of central tendency and dispersion were performed for continuous variables and absolute frequency for categorical variables. The Statistical Package for Social Sciences (SPSS), version 21.0, was used for data analysis.

This study was approved by the Research Ethics Committee (*Comitê de Ética e Pesquisa* – CEP) of INCA under number 4.702.209.

RESULTS

We included 362 patients, with a mean age of 58.17 (±12.16) years. Most were women (98.9%), self-reported to be Black and/or mixed-race (63.0%), did not live with a partner (57.7%), had level of education equal to or greater than eight years of formal education (69.0%), had household chores as the main occupation (69.3%), and resided in the "Metropolitana I" region of the state of Rio de Janeiro (RJ), Brazil (91.4%)[14] (Table 1).

At the time of breast cancer diagnosis, 73.7% of patients were classified with locally advanced clinical staging (≥IIB), but at the time of one-year postoperative teleconsultation, only 2.8% presented disease progression. Regarding surgical treatment, 82.3% of the patients underwent mastectomy and 88.1% underwent axillary lymphadenectomy. Only 3.1% of women submitted to mastectomy underwent immediate breast reconstruction with silicone prosthesis or tissue expander. Most were submitted to chemotherapy (89.0%), radiotherapy (88.7%), and hormone therapy (86.7%); and only 15.8%, to molecularly targeted therapy (Table 1).

At the time of the one-year teleconsultation, 82.3% of the patients were under treatment with hormone therapy; 3.0%,

radiotherapy; 3.0%, chemotherapy; and 4.1%, molecularly targeted therapy (Table 2).

Among the complications reported in the one-year physical therapy teleconsultation, the most frequent was paresthesia in the ICBN (87.1%); 23.8% of the patients reported pain and 22.1%, phantom breast sensation. The subjective sensation of lymphedema was reported by 4.1% of the patients and 6.9% noticed changes in the volume of HUL, characterizing lymphedema (Table 3).

As for life habits, most patients reported to be independent for personal care (99.7%), of which 79.3% carried out household chores alone, without assistance. Home exercises with upper limbs (UL), according to postoperative guidelines, were present in 83.1% of the population, with regular frequency of 50.1%. As for physical exercises, only 28.7% of the patients practiced them (Table 4).

During the teleconsultation, 43 women (11.9%) were referred to face-to-face evaluation at the HCIII/INCA physical therapy outpatient clinic (non-tabulated data). Regarding the reason for referral, 58.1% (n=25) reported lymphedema, due to the perception of alteration in the volume of HUL. Other complications confirmed in the face-to-face evaluation are shown in Table 5.

Table 1. Sociodemographic, clinical, and treatment data of the study population (n=362).

Variables	n (%)[a]	Variables	n (%)
Age (mean and SD)	58.17 (±12.16)	**Disease progression***	
		No	352 (97.2)
		Local recurrence	3 (0.8)
		Distant metastasis	7 (2.0)
Sex		**Breast surgery**	
Women	358 (98.9)	Conservative	63 (17.4)
Men	4 (1.1)	Mastectomy	298 (82.3)
		No approach**	1 (0.3)
Skin color		**Axillary approach**	
Black and/or mixed-race	228 (63.0)	SLNB	43 (11.9)
White	134 (37.0)	AL	319 (88.1)
Marital status		**Immediate breast reconstruction*** **	
Have a partner	153 (42.3)	No	285 (96.9)
No partner	209 (57.7)	Yes	9 (3.1)
Level of education*		**Chemotherapy**	
<8 years	110 (31.0)	No	40 (11.0)
≥8 years	247 (69.0)	Yes	322 (89.0)
Occupation		**Radiotherapy**	
Housewife	251 (69.3)	No	41 (11.3)
Outside job	111 (30.7)	Yes	321 (88.7)
Residence region (RJ)			
Metropolitana I	331 (91.4)	**Hormone therapy**	
Metropolitana II	19 (5.2)	No	48 (13.3)
Serrana	7 (2.0)	Yes	314 (86.7)
Baixada litorânea	4 (1.1)		
Médio Paraíba	1 (0.3)		
Clinical staging		**Targeted therapy**	
0-IIA	95 (26.3)	No	305 (84.2)
≥IIB	266 (73.7)	Yes	57 (15.8)

SD: standard deviation; SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; RJ: Rio de Janeiro. *Patients who were under treatment due to progression of the disease at the time of the one-year teleconsultation; **exclusive axillary lymphadenectomy, without breast approach, for occult breast cancer; ***the difference in the total sample is due to the total number of women undergoing mastectomy; [a]the total value may change due to missing values.

DISCUSSION

In this study, we identified that the main symptom reported by patients in the one-year teleconsultation after breast cancer surgery is paresthesia in the ICBN (87.1%), characterized by alteration of sensitivity in the medial region of the arm, axilla, and lateral trunk resulting from nerve injury[15,16].

As ICBN has close connection with axillary lymph nodes, the risk of injury is high during lymph node dissection[16]. The diagnosis of ICBN injury is clinical and, although numbness is very common, several events may occur in the distribution of the nerve due to changes in its function, such as tingling, burning and electrical sensations, in addition to pain[15,16].

According to Andersen *et al.*[17], hypoesthesia was the main sensory dysfunction one year after surgery, affecting 85.0% of patients. The authors also sought a relationship between surgical treatment and sensory dysfunction, and observed that the areas of hypoesthesia were significantly greater for patients treated with mastectomy ($p<0.0001$) and axillary lymphadenectomy (AL; $p<0.0001$) compared to those treated with conservative surgery and sentinel lymph node biopsy (SLNB).

Table 2. Treatment in progress at the time of the one-year teleconsultation after breast cancer surgery (n=362).

Variables	n (%)*
Treatment in progress	
No	52 (14.4)
Adjuvant	300 (82.9)
Palliative	10 (2.8)
Hormone therapy	
No	64 (17.7)
Yes	298 (82.3)
Chemotherapy	
No	351 (97.0)
Yes	11 (3.0)
Radiotherapy	
No	351 (97.0)
Yes	11 (3.0)
Targeted therapy	
No	347 (95.9)
Yes	15 (4.1)

*The same patient could be undergoing more than one treatment simultaneously, except in cases of chemotherapy and hormone therapy or chemotherapy and radiotherapy.

Lucena *et al.*[18] carried out a cross-sectional cohort in the same institution of the present study and evaluated 182 women after one year of surgical treatment for breast cancer; they observed that 58.2% of the interviewees reported paresthesia in the ICBN. However, in the aforementioned study, the majority of patients only underwent SLNB (58.2%), while in our study the vast majority were submitted to AL (88.1%).

In the study by Siqueira *et al.*[19], 47.2% of the interviewees reported sensory alteration related to ICBN injury after the mean time of 5.06 years (±1.8) between surgery and evaluation. The difference in the results can be justified by the fact that the evaluation of patients in the research of Siqueira *et al.*[19] was carried out in a longer interval, in addition to a higher percentage of SLNB (39.8%), compared to the present study.

Persistent pain or painful syndrome after treatment of breast cancer related to intercostobrachial neuralgia (pain in the ICBN) or in the phantom breast is another common symptom, affecting 25–60% of patients, and has been associated with a decrease in quality of life.

In addition to surgery, adjuvant therapies, such as radiotherapy and systemic treatments, are also risk factors for painful syndrome, as they can cause damage to nerve fibers[20-22].

In the study sample, 23.8% of the patients complained of pain at the time of the physical therapy teleconsultation, most related to the upper limb homolateral to surgery (14.4%). Pain was the second most frequent reason (41.8%) for referral of patients to face-to-face outpatient consultation.

Authors of a meta-analysis comprised of 18 observational studies with 6,364 patients with persistent pain after breast cancer surgery found that the prevalence of this symptom was 31.0% (95%CI: 23–41%) in 1–2 years[23].

The complication responsible for the highest number of referrals to face-to-face consultation after one year of surgery

Table 3. Complications reported in the one-year teleconsultation after breast cancer surgery (n=362).

Variables	n (%)*[a]
Paresthesia in the ICBN	
No	47 (12.9)
Yes	312 (87.1)
ICB	
No	347 (96.9)
Yes	11 (3.1)
AWS	
No	357 (98.6)
Yes	5 (1.4)
ROM	
No	359 (99.2)
Yes	3 (0.8)
Pain	
No	276 (76.2)
Yes	86 (23.8)
Pain site	
HUL	52 (14.4)
Chest wall/breast/thorax	17 (4.7)
Other	17 (4.7)
Does not apply	276 (76.2)
Phantom breast	
No	198 (56.9)
Yes	77 (22.1)
Does not apply**	73 (21.0)
Subjective sensation of lymphedema	
No	347 (95.9)
Yes	15 (4.1)
Lymphedema	
No	337 (93.1)
Yes	25 (6.9)

ICBN: intercostobrachial nerve; ICB: intercostobrachial neuralgia; AWS: axillary web syndrome; ROM: reduced range of motion; HUL: homolateral upper limb. *Each patient may have presented more than one complication; **women undergoing conservative surgery and immediate breast reconstruction; [a]the total value may change due to missing values.

Table 4. Life habits and home routine at the time of the one-year teleconsultation after breast cancer surgery (n=362).

Variables	n (%)[a]
Independence in personal care	
Yes	361 (99.7)
No	1 (0.3)
Household chores	
Carries it out completely	287 (79.3)
Carries it out partially	73 (20.2)
Does not carry it out	2 (0.6)
Practice of home exercises with UL	
Yes	301 (83.1)
No	61 (16.9)
Frequency of home exercises with UL	
Regular*	181 (50.0)
Irregular	120 (33.1)
Never	61 (16.9)
Practice of physical exercises	
Yes	100 (28.7)
No	248 (71.3)

UL: upper limbs. *At least once a day; [a]the total value may change due to missing values.

Table 5. Complications confirmed in the face-to-face consultation (43 women).

Variables	n (%)*
Lymphedema	25 (58.1)
Pain	18 (41.8)
Paresthesia in the ICBN	2 (4.6)
AWS	1 (2.3)
ROM	1 (2.3)

ICBN: intercostobrachial nerve; AWS: axillary web syndrome; ROM: reduced range of motion. *Each patient may have presented more than one complication.

was lymphedema, reported by 25 women (6.9% of the sample), through the perception of alteration in the volume of HUL. This prevalence was confirmed in the face-to-face evaluation.

According to recent research, the incidence of lymphedema after surgical treatment of breast cancer varies according to the characteristics of the studied population, being associated, in general, with high body mass index/obesity, a higher number of lymph nodes removed, radiotherapy on the lymph node chain, and taxane-based chemotherapy[24-26].

In the study by Furlan *et al.*[27], whose objective was to evaluate the circumference and the sensation of swelling in the upper limb homolateral to surgery right after the procedure and within 24 months, the authors identified that, in the first year, of the 152 patients followed up, 23.7% had a feeling of limb edema; 21.1% had a difference greater than 2 cm at a single point; and 5.9%, circumference greater than 2 cm at two points, comparing the affected limb and contralateral limb.

In the present study, in the one-year teleconsultation, only 4.1% of patients reported a subjective sensation of lymphedema and 6.9% (n=25) reported lymphedema because they noticed changes in the volume of the affected limb, which was confirmed in all of these 25 patients in the face-to-face evaluation.

Konish *et al.*[28] found cumulative incidence of lymphedema in high-risk patients of approximately 3.0% in one year. Conversely, in the study by Paramanandam *et al.*[29], of the 149 patients guided as for the usual care with arm, skin, drain, and daily shoulder exercises since the first postoperative day, the cumulative incidence in one year was 25.0%. When evaluating 580 patients submitted to breast surgery and postoperative radiotherapy with or without systemic treatment, Kim *et al.*[30] found a cumulative incidence of 10.5% after one year of radiotherapy, but in this sample the majority of patients (84.5%) underwent conservative breast surgery and sentinel lymph node biopsy (78.4%), and less than half of the patients (37.4%) did not receive chemotherapy.

In the cohort study conducted by Fabro *et al.*[31], on 174 women with a mean age of 58 years, 29.5% of the patients reported the subjective sensation of edema in the upper limb homolateral to surgery after approximately eight months postoperatively, corroborating our findings, although the evaluation time was slightly shorter in the aforementioned study[31].

ICBN paresthesia and lymphedema were also the most common complications found in the study conducted by Abass *et al.*[32] In a sample of 96 patients, the authors identified paresthesia as the most frequent complication (21.9%), followed by lymphedema (9.4%), in the average time of 18 months of follow-up.

Although most patients in the present study reported total independence for personal care (99.7%) and carrying out household chores, without assistance (79.3%), demonstrating being active in the day-to-day, when questioned about the practice of exercises with the UL, 83.1% stated practicing them as recommended since the physical therapy consultation of the first postoperative day, but half of these (50.0%) followed a regular routine (at least once a day). Only 28.7% of the interviewees reported practicing some kind of sport activity at the time of teleconsultation.

Marchito *et al.*[33] also observed that patients submitted to surgical treatment of breast cancer adhere to the preventive physical therapy guidelines (skin care and exercise with UL) after surgery, especially in the early months, and that adherence to these guidelines reduced in the following months, mainly due to household chores.

Lee *et al.*[34], in a study carried out in Malaysia on the practice of global physical activity by breast cancer survivors, found that physical activity levels in this population were inadequate since diagnosis and that they significantly reduced (p=0.04) over three years after cancer discovery. Among the interviewees, 48.1% were active at the time of diagnosis, 39.8% in one year, and 35.3% in the third year.

Groef *et al.*[35] assessed the levels of global physical activity within two years after breast cancer surgery and found that in none of the domains (occupational, sports, and domestic) there was a return to preoperative activity levels.

The studies whose authors address teleconsultation as a modality of care show that this strategy is effective, accessible, and viable for monitoring patients in breast cancer treatment. Singleton *et al.*[36] suggested that interventions through teleconsultation had wide range, high acceptance by survivors of breast cancer, and were effective in improving quality of life, self-efficacy, fatigue, and psychological suffering.

Nápoles *et al.*[37] found positive evidence related to viability, acceptability, and efficacy, with significant improvement in fatigue, psychological suffering, and emotional well-being as well as benefits related to greater knowledge of recommended care. The authors also observed an improvement in symptoms and in the level of physical activity in breast cancer survivors. Macedo *et al.*[13] evaluated patients' opinion on teleconsultations for follow-up of breast cancer, and showed good acceptance with patients feeling safe, satisfied, and comfortable.

A recent guideline on telerehabilitation in patients with breast cancer suggests that this modality is present from the initial moments of the preoperative period and through individualized programs, with prescription of exercises in the postoperative and at the long term[38]. Moreover, authors of systematic reviews have shown that this form of care is cost-effective in public health, especially for people living in rural areas[39,40].

Although this is a cross-sectional study, with no information since the preoperative period, its strength is presenting the prevalence of the main complications one year after breast cancer surgery evaluated through teleconsultation. The predominant symptoms or complications described in this period may guide physical therapists and other healthcare professionals in their medium- and long-term conduct. In addition, we showed that the number of face-to-face consultations required after teleconsultation was low, which makes the online modality a viable resource after surgical treatment of breast cancer.

CONCLUSIONS

The most frequent complications reported by patients in the one-year teleconsultation after breast surgery were paresthesia, pain, and phantom breast sensation. The greatest reason for referrals to face-to-face consultation was lymphedema, with diagnostic confirmation of all cases. With such findings, this modality of care shows a possibility of effective follow-up in the postoperative period of breast cancer.

AUTHORS' CONTRIBUTION

JFC: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. FOM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. EANF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. FOF: Data curation, Investigation, Writing – original draft, Writing – review & editing. DMT: Data curation, Investigation, Writing – original draft, Writing – review & editing. JFOTO: Data curation, Investigation, Writing – review & editing. SAS: Data curation, Investigation, Writing – review & editing. RMC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
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A prospective evaluation of breast satisfaction and expectation in preoperative immediate breast reconstruction patients**

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ABSTRACT

Introduction: Breast reconstruction has an important positive contribution to the quality of life of breast cancer patients. However, a large proportion of breast cancer survivors have unmet expectations surrounding reconstruction. This study aimed to delineate factors affecting preoperative native breast satisfaction and expectations with surgery in immediate breast reconstruction (IBR) patients. **Methods:** This is a prospective cross-sectional trial with breast cancer patients undergoing oncology surgery following breast reconstruction enrolled from 2019 to 2021 at the Hospital Nossa Senhora das Graças in Curitiba, Brazil. Two groups were studied: patients who underwent mastectomy following IBR with implant; and those who underwent breast conservative therapy (BCT) following oncoplastic surgery (OP). All patients completed a patient-reported outcome, the BREAST-Q Breast Reconstruction Expectations Module, prior to surgery. **Results:** Seventy-nine patients with breast cancer were included: 49 OP and 30 mastectomy following IBR. The mastectomy with IBR implants group had a better satisfaction with their native breast than the OP group (p=0.001). Women in the OP group had higher expectations for breast appearance when clothed than the mastectomy with IBR implant group (p=0.030). Patients aged 50 years and older with a university education or higher level expected that their breast appearance would match almost the same after ten years (p=0.001). **Conclusions:** Our results highlight the importance of establishing realistic expectations prior to surgery. Understanding which factors affect patients' satisfaction with native breasts and their expectation toward surgery in the preoperative set could improve preoperative counseling and management of patients' expectations regarding breast reconstruction.

KEYWORDS: expectation; breast reconstruction; satisfaction; quality of life; breast cancer.

INTRODUCTION

Breast cancer care involves highly complex procedures such as surgery in conjunction with oncoplastic techniques and breast reconstruction[1,2]. Over the past 20 years, there have been many innovations and advancements that elevate the quality of breast reconstruction following a mastectomy or breast conservative surgery. Several methods and surgical techniques were developed such as tissue expanders; shaped, integrated valve; textured saline or silicone gel implants that have undergone significant improvements; a novel and innovative oncoplastic approach described based upon an oncoplastic algorithm; fluorescent laser angiography; acellular dermal matrices; and current techniques for fat grafting that have revolutionized breast reconstruction. These advancements focus on improving surgical and aesthetic outcomes as well as reducing adverse events[3].

There is general agreement that breast reconstruction makes a significant positive contribution to the quality of life of many women who have undergone mastectomy for breast cancer[4-6]. Patients' satisfaction is one of the most important endpoints whose overriding goal is to meet their expectations and improve their quality of life. However, a large proportion of breast cancer survivors have unmet expectations surrounding reconstruction after mastectomy, particularly in relation to appearance. Approximately 42% of women who underwent breast

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reconstruction after mastectomy reported their reconstruction to be worse than expected[7].

There is little consensus about what impact specific factors have on women`s satisfaction with the breast reconstruction process and outcomes. Concerning expectation and satisfaction issues, several instrumentals were validated but most of them are general questionnaires that do not specify body and psychological changes experienced by breast cancer patients[8,9] and compare different surgical approaches. Among the available patient-reported outcome measurement tools, the BREAST-Q has established itself as the gold standard, being most frequently used in the literature[10-12]. The BREAST-Q questionnaire was developed especially for breast cancer patients undergoing breast surgery. Independent modules are available for different surgical interventions (e.g., mastectomy, breast reconstruction, or conservative surgery). Each module consists of a preoperative and a postoperative questionnaire[13]. In 2012, a specific preoperative expectation for breast reconstruction module was added to the BREAST-Q set of questionnaires that cover a range of breast surgical procedures. The expectation module covers a thorough range of questions about how the patient expects to feel in the first week, first year, and ten years after breast reconstruction surgery[4].

A preoperative assessment of quality of life, satisfaction, and expectation can aid the surgeon in an accurate clinical evaluation and may allow for early identification of patients with a higher risk of regret[14,15]. Furthermore, these assessments improve patient education, shared medical decision-making, patient perception of outcomes[16], and provide a point of reference for assessing change after a procedure[15]. Besides, it is an important predictor of health outcomes and health-related quality of life[16,17]. Unrecognized or unfilled expectations have been shown to correlate with patients' low satisfaction and poor overall outcomes in any type of surgery[17-20]. Despite its importance, few studies to date have focused on measuring expectations and satisfaction prior to oncological breast surgery using systematically the validated BREAST-Q[21]. A systematic review of literature did not find consistent evidence to support a link between patients' expectations and degrees of satisfaction with breast reconstruction outcomes[4]. A recent study that evaluated patients' expectations using the preoperative BREAST-Q expectation score was a retrospective chart review that included mainly delayed reconstruction[17].

The present study aimed to delineate factors affecting preoperative native breast satisfaction and expectations toward surgery using the BREAST-Q in patients before oncological breast surgery following IBR.

METHODS

This is a prospective cross-sectional trial with breast cancer patients undergoing oncology surgery (mastectomy or breast conservative therapy) following breast reconstruction or oncoplastic surgery enrolled from November 2019 to October 2021 at the Hospital Nossa Senhora das Graças, Breast Unit, in Curitiba, Brazil. All patients had ***in situ*** or invasive carcinoma diagnosed by core biopsy or vaccum-assisted biopsy[9]. We excluded patients who refused participation in the study, who would undergo prophylactic mastectomy or preoperative radiotherapy, and those who had local recurrence or metastasis at the time of analysis[9].

Two independent groups of patients undergoing oncology surgery were studied. The first included patients who underwent mastectomy following IBR with definitive anatomical form-stable implant. Here, contralateral symmetrization was performed using different techniques according to the necessity in each individualized case and the possibility of obtaining better symmetry with the reconstructed breast: reduction mammaplasty, mastopexy, augmentation mammaplasty, or mastopexy associated with implant[9]. The second group underwent breast conservative therapy (BCT) following level 2 oncoplastic techniques (bilateral surgeries with mammaplasty techniques).

This study was approved by the Internal Review Board of Positivo University, Curitiba, Brazil, on September 19, 2019.

All patients were invited to complete the patient-reported outcome BREAST-Q Expectations Module and Preoperative Breast Reconstruction or Preoperative Reduction/Mastopexy Module already translated into Portuguese. They signed informed consent and answered the questionnaire in paper format prior to the surgical procedure.

The BREAST-Q Preoperative Breast Reconstruction Module comprises two domains: satisfaction (i.e., satisfaction with breasts) and quality of life (psychosocial, physical, and sexual well-being), consisting of five scales. The score from each scale is transferred into a 100-point scale. Thus, BREAST-Q question values were transformed and scored using the QScore, a statistical program developed specifically for the BREAST-Q that provides a total scale score, ranging from 0 to 100, in which a higher score suggests a better quality of life or satisfaction[8-10].

The BREAST-Q Preoperative Expectation short-form module is composed of five scales and assesses:

1. Pain;
2. Appearance when clothed after one year;
3. Appearance of breast symmetry after one year;
4. Sensation of breast after one year; and
5. Appearance of breast symmetry after ten years.

Response options for all scales are on a 3-point Likert-type scale, where 1 represents unlikely, 2 likely, and 3 very likely[17].

Item responses for each section of the modules are summed and transformed to give a score for each scale (0–100), using a standardized conversion template[17]. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) program. For quantitative variables, expressed with mean ± standard deviation, the Mann-Whitney U test was applied. For

qualitative variables, expressed with numbers and percentages, Fisher`s exact test was used. Sociodemographic and clinical characteristics were compared between groups. A p<0.050 was considered statistically significant.

RESULTS

Overall, 79 breast cancer patients completed the preoperative BREAST-Q questionnaire. Patients were divided into two groups: BCT following oncoplastic surgery (n=49) and mastectomy following IBR with implant (n=30). Table 1 summarizes the sociodemographic characteristics of the cohort. The mean age was 52.6 standard deviation±12.3 years. Most patients were considered overweight or obese (64.5%) and 16 women had previously been submitted to breast aesthetic surgery (20.3%).

Table 2 shows BREAST-Q expectation and satisfaction rates for both groups. The mastectomy with IBR implants group had a better satisfaction with their native breasts than BCT oncoplastic group (p=0.001). There was no statistically significant difference between groups regarding the other parameters.

When we compared BREAST-Q reconstruction expectations rate, women in BCT following oncoplastic group had higher expectations for breast appearance when clothed than the mastectomy with IBR implant group (93.4±16,3 vs. 82.9±26.5; p=0.030).

Table 1. Sociodemographic characteristics of study cohort.

Characteristic	BCT+Oncoplastic n (%)	Mastectomy with IBR implants n (%)	p-value
Age, mean±SD (year)	52.3±12.8	53±11.6	0.82
BMI, mean±SD	27.4±4.7	25.5±4.1	0.07
Weight characteristics			
Normal	14 (28.6)	14 (46.7)	0.16
Overweight	26 (53.1)	14 (46.7)	
Obese	9 (18.4)	2 (6.7)	
Menopausal status			
Postmenopausal	25 (51.0)	17 (56.7)	0.65
Premenopausal	24 (49.0)	13 (43.3)	
HRT			
Yes	16 (32.7)	9 (30.0)	1.00
No	33 (67.3)	21 (70.0)	
Education level			
Unfinished primary school	5 (10.2)	1 (3.3)	0.81
Full primary school	1 (2.0)	2 (6.7)	
High school	9 (18.4)	7 (23.3)	
College degree	18 (36.7)	6 (20.0)	
Specialization, postgraduate degree	16 (32.7)	14 (46.7)	
Family history			
Yes	24 (49.0)	13 (43.3)	0.65
No	25 (51.0)	17 (56.7)	
Previous aesthetic breast surgery			
Yes	7 (14.3)	9 (30.0)	0.15
No	42 (85.7)	21 (70.0)	
Neoadjuvant chemotherapy			
Yes	17 (34.7)	9 (30.0)	0.81
No	32 (65.3)	21 (70.0)	
Smoking			
Yes	3 (6.1)	5 (16.7)	0.25
No	46 (93.9)	25 (83.3)	

BCT: breast conservative therapy; IBR: immediate breast reconstruction; SD: standard deviation; BMI: body mass index; HRT: hormonal reposition therapy.

Table 2. BREAST-Q satisfaction and expectation rates between the two groups.

BREAST-Q satisfaction			
	BCT+Oncoplastics (n=49)	Mastectomy with IBR implants (n=30)	p-value
	Mean±SD	Mean±SD	
Psychosocial well-being	55.5±16.7	71.9±23.0	0.920
Sexual well-being	61.3±23.0	61±21.6	0.950
Physical well-being	69.1±16.4	68.2±22.4	0.850
Satisfaction with breast	55.5±16.7	71.9±23	**0.001**
BREAST-Q expectations			
	BCT + Oncoplastics (n=49)	Mastectomy with IBR implants (n=30)	p-value
	Mean±SD	Mean±SD	
Expectations for pain	63.2±18.9	56.7±23.9	0.190
Expectations for breast appearance when clothed	93.4±16.3	82.9±6.5	**0.030**
	n (%)	n (%)	p-value
Expectation for breast appearance when unclothed after one year			
Will look very different	1 (2.0)	0 (0.0)	0.623
Will look similar	35 (71.4)	24 (80.0)	
Will look exactly the same	6 (12.2)	4 (13.3)	
Don't know	7 (14.3)	2 (6.7)	
Expectations for breast sensation after one year			
Almost no sensation	3 (6.1)	6 (20.0)	**0.001**
Will have some sensation	10 (20.4)	13 (43.3)	
Will have normal sensation	25 (51.0)	3 (10.0)	
Don't know	21 (42.9)	8 (26.7)	
Expectation for breast appearance after ten years			
Will not match	9 (18.4)	6 (20.0)	0.721
Will match almost	21 (42.9)	11 (36.7)	
Will match exactly	3 (6.1)	4 (13.3)	
Don't know	16 (32.7)	9 (30.0)	

BCT: breast conservative therapy; IBR: immediate breast reconstruction (implant based); SD: standard deviation.
Bold indicates statistically significant p-values.

Most patients in both groups expected that breast appearance (symmetry) when unclothed would look similar after one year (71.4% for BCT and 80.0% for mastectomy group) and after ten years would match almost the same as it did right after the reconstruction (42.9% for BCT and 36.7% for mastectomy group). In the BCT with oncoplastic group, 51.0% of patients expected that the breast would have normal sensation after one year, whereas 43.3% of women in the mastectomy with IBR group expected to have some sensation (p=0.001).

Table 3 shows logistic regression analysis and results. Previous aesthetic breast surgery and neoadjuvant chemotherapy were significant predictors of preoperative physical well-being. Patients 50 years or older and with a university degree or higher level of education expected that their breast appearance would match almost the same after ten years (p=0.001) (Table 4).

DISCUSSION

Patients' satisfaction with their breasts is an important metric for the evaluation of outcomes in breast surgery[15]. Many factors affect aesthetics and satisfaction with each native breast; it is difficult to capture in existing assessments. In our study, the mastectomy with IBR implant group had better satisfaction with their native breast than the BCT oncoplastic group (p=0.001). Despite all these variables and nonspecific factors, it is essential to have baseline scores representative of patients' self-perception (15) before treatment in order to assess whether quality of life will change postoperatively.

Patients in the oncoplastic group had worse preoperative psychosocial well-being (55.5±16.3) than the breast reconstruction group (71.9±23.0), and in both groups, we found low physical well-being scores. It is important to consider that preoperative

Table 3. BREAST-Q satisfaction and reconstruction expectations according to different factors.

	Psychosocial well-being	Sexual well-being	Physical well-being	Satisfaction with breast	Expectations for pain	Expectations for breast appearance when clothed
Age (years)						
<39	73.8±18.3	67.6±17.2	70.1±23.2	65.0±18.9	70.0±14.7	87.5±21.6
40–49	66.7±19.9	55.2±22.4	64.1±17.3	55.7±19.2	64.4±19.7	91.6±15.5
50–59	66.9±19.4	64.4±19.7	69.0±17.7	66.0±20.6	63.4±18.0	84.4±29.6
>60	76.0±20.2	61.3±27.6	72.6±19.1	61.6±23.3	49.5±24.7	93.3±15.6
p-value	0.31	0.40	0.51	0.37	0.26	0.53
Educational level						
High school or less	68.7±23.4	57.4±27.8	69.3±20.1	60.6±21.8	54.1±20.6	92.5±16.0
University or more	71.1±18.0	62.9±19.7	68.6±18.3	62.1±20.5	63.4±21.0	88.2±23.0
p-value	0.62	0.33	0.89	0.78	0.90	0.42
Previous aesthetic breast surgery						
Yes	73.7±18.6	70.9±18.1	77.2±15.1	68.4±22.8	53.4±27.7	82.9±29.1
No	69.5±20.1	58.8±22.9	66.6±19.1	59.9±20.1	62.8±18.7	91.1±18.6
p-value	0.45	0.06	0.044*	0.14	0.11	0.17
Weight characteristic						
Normal	75.5±20.5	65.9±22	74.3±18.0	65.7±20.4	62.9±19.7	90.0±18.4
Overweight	65.9±18.6	57.9±24.6	64.9±17.7	59.7±21.9	59.7±21.9	90.7±21.8
Obese	73.6±19.4	60.1±12.1	69.6±21.8	60.6±12.8	58.5±23.5	84.2±25.8
p-value	0.12	0.37	0.12	0.43	0.78	0.66
Neoadjuvant chemotherapy						
Yes	65.3±19.9	55.6±24.9	62.7±14.7	60.5±21.2	65.0±18.4	92.4±15.1
No	72.9±19.3	64.1±20.6	71.7±19.8	62.3±20.7	58.5±22.2	88.0±23.6
p-value	0.11	0.12	0.04*	0.67	0.21	0.40

*Statistically significant (p<0.050).

patients are not "normal", as they have undergone the physical and psychological trauma associated with being diagnosed with breast cancer[22] — a unique entity and a life-changing moment for each patient. The low physical well-being score may be explained by pain secondary to the tumor itself or pain after biopsy before cancer resection[22]. A study by Roth et al.[23] showed that women who reported higher preoperative levels of distress and anxiety were significantly less satisfied with the outcomes of breast reconstruction[23,24]. Clearly, many clinical and non-clinical factors influence a woman's satisfaction with psychosocial and physical breast reconstruction outcomes, making a single measurement of satisfaction challenging[4]. Differently, Builes Ramírez et al. identified no anthropometric and clinical variables related to satisfaction and quality of life in breast cancer women before their surgical procedure[25]. In our study, we found that variations in expectations such as previous aesthetic breast surgery and neoadjuvant chemotherapy were significant predictors of preoperative physical well-being.

The assessment and management of patients' expectations may improve their perception of outcomes[16]. When we compare the two different types of surgery, in the BCT with oncoplastic group, 51.0% of patients expected that the breast would have normal sensation after one year, whereas 43.3% of women in mastectomy with IBR group expected to have some sensation (p=0.001). A review by Sisco et al.[26] reported that sensory outcomes in nipple-sparing mastectomy varied, with normal sensation self-reported in the range 10.0–43.0%[26,27]. However, it has now become clear that nipple sensation is largely or completely lost in most cases. A Swedish prospective study that quantitatively examined tactile, thermal, and nociceptive cutaneous sensitivity before and after nipple-sparing mastectomy found total loss of touch sensation in the nipple in 62.0% of patients, while touch sensation was impaired in the remaining 38.0%[27,28]. These findings highlight the importance of managing patients' expectations about breast and nipple sensations after mastectomy to reduce the risk of dissatisfaction with the surgery.

Interestingly, we identified that most women in both groups expected that breast appearance (symmetry) when unclothed would look similar after one year (71.4% for BCT and 80.0% for

Table 4. Analysis of BREAST-Q reconstruction expectation for breast appearance after ten years according to different factors.

	Expectation for breast appearance after ten years				
	Will not match	Will match almost	Will match exactly	Don't know	p-value
Age (years)					
<39	4	6	0	1	0.03*
40–49	5	7	0	12	
50–59	5	9	2	6	
>60	1	10	5	6	
Educational level					
High school or less	2	9	1	13	0.04*
University or more	13	23	6	12	
Previous aesthetic breast surgery					
Yes	6	6	2	2	0.09
No	9	26	5	23	
Weight characteristic					
Normal	8	13	2	5	0.18
Overweight	6	17	3	14	
Obese	1	2	2	6	
Neoadjuvant chemotherapy					
Yes	6	11	0	9	0.27
No	9	21	7	16	

*Statistically significant (p<0.050).

mastectomy group) and after ten years would match almost the same as it did right after reconstruction (42.9% for BCT and 36.7% for mastectomy group). Overall, the aesthetic outcomes decline over time, especially if chemotherapy and radiotherapy are required. Furthermore, breast cancer patients using adjuvant endocrine therapy can vary their weight resulting in asymmetry, impacting patient-reported outcomes. In breast-conserving therapy, a prospective study by Hennigs et al.[29] showed that the change in the aesthetic outcome is still measurable over four years after the surgical procedure with a subjective evaluation[29,30]. In breast reconstruction with implant, several authors have described a trend of deterioration over time, with a decline in aesthetic outcomes, an increase in capsular contracture, and an overall decrease in patient satisfaction[10,31,32]. Seth and Cordeiro contradict these results demonstrating that prosthetic breast reconstruction outcomes do not deteriorate over time. This stability is apparent in both long-term surgeon and patient report outcomes data measured in the same patients[10]. Despite the differences in the literature, we delineated factors such as patients aged 50 years and older with university education or higher who expect their breast appearance to match almost the same after ten years (p=0.001). These findings emphasize the importance of managing patient expectations about breast and nipple sensation after mastectomy and aesthetic outcomes over time to reduce the risk of dissatisfaction with the surgery.

It is important to consider that most data were collected during the coronavirus disease (COVID-19) that was first reported in Wuhan (China), in December 2019. The COVID-19 pandemic became one of the main international concerns regarding its impact on mental health[33]. A study that included 3,000 Brazilian population from 25 states showed that almost half of participants expressed symptoms of depression (46.4%), anxiety (30.7%), and stress (42.2%) in this period[33]. Mental illness during the pandemic associated with the diagnosis of breast cancer may have adversely affected the satisfaction and quality of life scores found in our study.

A strength of this work is that it is the first prospective study that provides a useful perspective on the patients' feelings prior to breast cancer surgery, using the objective, validated, and reliable BREAST-Q questionnaire. The recruitment of this population included all breast cancer patients who underwent oncological surgery with IBR or oncoplastic surgery. We excluded those who underwent a prophylactic mastectomy and delayed breast reconstruction to get a homogenous cohort. This comparison enables surgeons to adopt an individualized approach according to the technique to be employed.

In contrast, this study also has several limitations. Our population was restricted to a single center, limiting the generalizability of data. As a cross-sectional study, there is an important element of selection bias to consider. We only included patients

who agreed to participate in the study; they probably had a better quality of life and satisfaction score than those who refused do take part.

Further studies are needed to evaluate the effect of preoperative patient expectations on patient-reported outcomes following breast reconstruction to determine whether preoperative expectations can be modified to produce long-term satisfaction after surgery. It is well documented that patients' satisfaction with their breasts correlates more strongly with their satisfaction with the information they received prior to surgery and with their plastic surgeon[24,34,35]. Failure to recognize and understand what patients expect from their surgical procedure often leads to dissatisfaction and poor overall outcome for them[24].

CONCLUSIONS

This study's results highlight the need to improve education and informed decision-making about breast reconstruction. Patients demonstrated high expectations for breast appearance after reconstruction and expected it not to change over time. Multiple factors influence preoperative breast satisfaction and expectation prior to surgery. Understanding which factors affect patients' satisfaction with native breasts and their expectations with the surgery in the preoperative set could improve preoperative counseling and the management of patients' expectations of subsequent breast reconstruction and reduce the risk of dissatisfaction with the surgery.

AUTHORS' CONTRIBUTIONS

FK: Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review and editing, Manuscript review. CAU: Conceptualization, Methodology, Project administration, Resources, Supervision, Manuscript review. MTD: Investigation, Validation, Visualization, Writing – original draft, Writing – review and editing. IR: Investigation, Validation, Visualization, Writing – original draft, Writing – review and editing. MRL: Data curation, Formal analysis, Software. BS: Data curation, Formal analysis, Software. ML: Conceptualization, Methodology, Project administration, Resources, Supervision, Manuscript review.

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ORIGINAL ARTICLE
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Trends in mastectomy performance for early breast cancer in a public institution with limited access: a retrospective cohort

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ABSTRACT

Objective: To assess trends in breast surgery, Breast-conserving surgery (BCS) and mastectomy, in an institution with limited access to health resources. **Methods:** A retrospective cohort study was carried out in patients who underwent surgery for non-metastatic breast cancer between 2012 and 2019 at the Hospital Geral de Fortaleza (HGF), an institution that exclusively treats patients from the Brazilian public health system (SUS). The main objective of the study was to evaluate the rates of mastectomy in the period, with or without immediate reconstruction, as well as BCS rates. The χ^2 test, with Bonferroni adjustment, was applied to the relative frequency of the procedures performed to test for statistical significance in the evolution of the frequencies of surgeries over the years. **Results:** A total of 805 patients underwent surgical treatment for non-metastatic breast cancer, with an average of 100 surgeries per year (range 85–118) during the study period. Mastectomy was performed in 552 cases (68.57%), while 253 patients underwent BCS (31.42%). Among the patients who underwent mastectomy, 181 (32.78%) had immediate reconstruction, with the highest proportion using implants (92.26%). No statistical difference was observed between mastectomies with or without reconstruction throughout the period (p=0.6635), with a statistically significant difference between BCS (p=0.04281) and mastectomies. **Conclusion:** There was no increase in the rates of mastectomies, with and without immediate reconstruction, over the years, but a trend towards an increase in BCS. Further studies are needed to better understand this trend in settings with limited access to health care.

KEYWORDS: breast neoplasms; mastectomy; mastectomy, subcutaneous; mastectomy, segmental; mammaplasty.

INTRODUCTION

Breast cancer is the most common malignant neoplasm in women, with an estimated 2 million cases annually worldwide[1,2]. In Brazil, the National Cancer Institute (INCA) estimates that there will be more than 73,000 cases of breast cancer in 2023[3]. The prognosis of the disease, on the other hand, has improved significantly in recent decades, with a significant impact on mortality. The advent of organized screening, significant improvements in cancer treatment, and a better understanding of biology are responsible for this impact[4,5].

Breast cancer surgery has evolved substantially over the years: there has been a gradual replacement of more radical techniques, such as the mastectomy proposed by Halsted, by less invasive approaches[6]. Breast-conserving surgery (BCS), associated with modern multimodal treatment, has similar local recurrence and overall survival rates compared to mastectomy[7,8]. However,

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despite the oncological safety of BCS, a trend towards increasing mastectomy rates, especially bilateral mastectomy, has been observed in developed countries in recent years. The advent of genetic knowledge, the possibility of immediate reconstruction and the false impression of greater safety have been related to the increase in mastectomy rates[9-14]. This trend, however, has not yet been adequately evaluated among patients with limited access to health care systems, where these technologies are not universally available.

The objective of this study was to characterize the trends in surgical procedures in non-metastatic breast cancer, especially mastectomies, with or without immediate breast reconstruction, compared to BCS, between 2012 and 2019, in a single Brazilian institution that provides exclusive treatment to patients of the Unified Health System (SUS).

METHODS

The main objective of this study was to analyze trends in mastectomy and BCS rates, between 2012 and 2019, in patients treated for non-metastatic breast cancer at the Hospital Geral de Fortaleza (HGF), a Brazilian public institution that provides care exclusively to patients covered by SUS. In Brazil, 80% of the population's medical care is provided by SUS. The study was initiated after approval by the institution's Research Ethics Committee (CAAE 29325720.7.0000.5040).

The records of surgical treatment of patients with breast cancer were evaluated, which included: BCS (with or without oncoplastic surgery), total mastectomy without immediate reconstruction, and mastectomy associated with immediate reconstruction, total or with preservation of the nipple-areola complex. The type of reconstruction performed, implants (permanent or temporary expanders) or myocutaneous flaps, and the specific date (year) of each procedure were also evaluated. The decision on each procedure was individually decided by the institution's breast surgeons, as well as the surgical technique used, including oncoplasty and the type of reconstruction. The institution's adjuvant and neoadjuvant treatments followed international guidelines. There was no genetic counseling or testing available during the study period. Patients with benign or indeterminate lesions, as well as other malignant breast lesions, such as melanoma or sarcoma, were excluded from the analysis, as were cases without adequate information on surgical treatment, clinical stage IV at the time of diagnosis or who did not undergo surgery.

Data were tabulated in a spreadsheet compatible with the SPSS-IBM version 20.0 application, used for data analysis. Data were expressed as absolute frequencies and percentages. The χ^2 test, with Bonferroni adjustment, was applied to the relative frequency of the procedures performed to determine the statistical significance in the evolution of frequencies by year. 95%CI with $p<0.05$ was used to determine the relationship of the variables with the trends in the rates measured during the study period under a log-linear model (Poisson regression).

RESULTS

After applying the study inclusion criteria, 805 patients undergoing surgical treatment for non-metastatic breast cancer were included for analysis. The average number of surgeries during this period was 100 procedures per year, ranging from 85 cases in 2012 to 118 in 2015 (Figure 1).

The most frequently performed surgical procedure was total mastectomy, in 552 cases (68.57%), while 253 patients underwent BCS (31.42%). In 2012, among the 85 surgeries performed, 44 (51.76%) cases were mastectomies without reconstruction, 19 (22.35%) mastectomies with reconstruction, and 22 (25.88%) BCS. On the other hand, in the last year of the analysis, in 2019, among 106 surgical procedures performed, 41 (38.68%) cases were BCS, 43 (40.57%) mastectomies without reconstruction, and 22 (20.75%) mastectomies with reconstruction. The year with the highest proportion of BCS was 2018 (n=41; 40.20%), while 2014 had the highest proportion of mastectomies (n=70; 81.40%). Among patients undergoing mastectomy, 181 (32.78%) had immediate reconstruction, where the highest proportion were with isolated implants (92.26%) and 14 cases with flaps (7.73%) (Figure 2).

When analyzing the evolution of mastectomies, no statistically significant increase in this procedure was observed over the period, nor was there a statistically significant difference between mastectomies with or without reconstruction (p=0.663). On the other hand, there was a statistically significant difference in conservative surgery over the years (p=0.042). Individually evaluating the proportions of each type of surgery during the study period, a statistically significant change was found only for conservative surgery (p=0.001; Bonferroni adjustment: p=0.003), compared to mastectomy without reconstruction (p=0.623; Bonferroni adjustment: p=0.299) and mastectomy with reconstruction (p=0.591; Bonferroni adjustment: p=0.663), as shown in Table 1. Finally, using

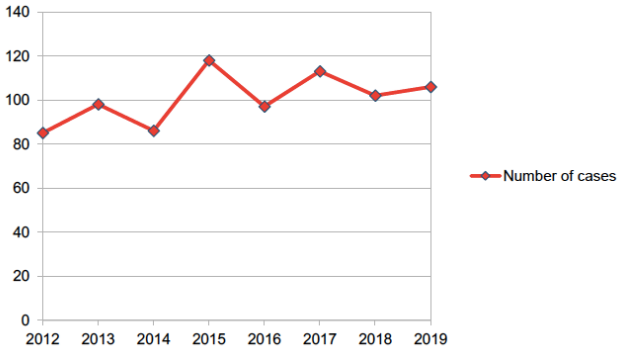

Figure 1. Evolution of total surgeries annually between 2012 and 2019.

Poisson regression, a variation in the profile of surgeries over the years was identified (<0.001), but without a significant difference between the types of surgery or immediate reconstruction (Table 2).

DISCUSSION

In this study, no overall increase in mastectomies was observed in an institution that treated patients in the Brazilian public system between 2012 and 2019. Conversely, an upward trend in BCS rates was observed throughout the study period. BCS is the preferred treatment for early breast cancer, replacing radical mastectomy in most cases, following the results of several randomized studies. A study from Denmark, for example, assessed the prevalence of BCS between 1982 and 2002, with an increase from less than 1% to 25% of conservative surgery, with a significant increase triggering the increase after the publication of the Danish Breast Cancer Cooperative Group study in 1988[15]. This trend, however, has recently changed in developed countries. A retrospective American study evaluated the temporal trend of mastectomies in more than 1 million women treated in centers accredited by the American Cancer Society and the American College of Surgeons Commission on Cancer between 1998 and 2011, using the National Cancer Database (NCDB), and it observed a 34% increase in mastectomies, with an odds ratio of 1.34 (95%CI 1.31–1.38)[14]. Other studies also identified an increase in bilateral mastectomies in the United States, with stability in conservative surgeries[12,13,16].

There are several hypotheses that may explain these differences, including the availability of immediate reconstruction. In Brazil, immediate breast reconstruction after mastectomy was guaranteed by a recent law for the public health system (Law No. 12,802, of 2013)[17]. However, in practice, it is possible that the impact has not yet been significant. In our analysis, only 32% of cases underwent immediate reconstruction, which may have affected the results, despite it being available in the institution.

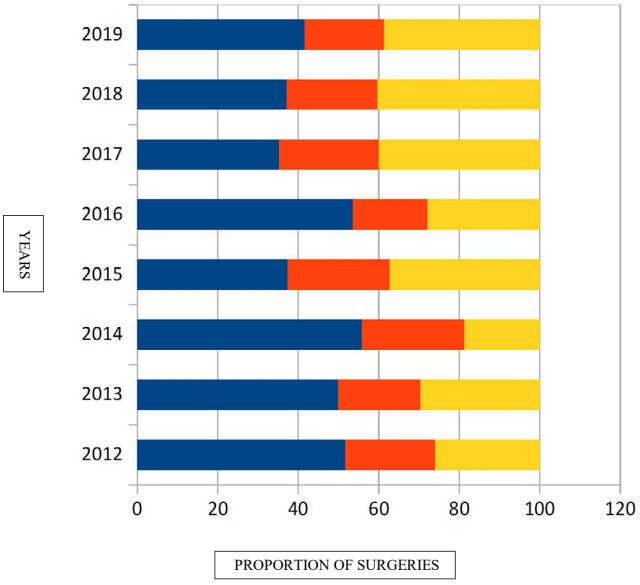

Figure 2. Proportion (%) of surgeries (breast-conserving therapy, in yellow; total mastectomy, in blue; and mastectomy and immediate reconstruction, in red) annually during the period of 2012 to 2019.

Table 2. Poisson regression for evaluation of surgeries annually.

	p-value
Year of surgery	<0.001
Type of surgery	
Mastectomy (No-BR + IBR)	0.907
BCS	1.000
Reconstruction	
No-BR	1.000
Implant	0.950
Myocutaneous flap	0.924

No-BR: Total mastectomy without reconstruction; IBR: Mastectomy and immediate reconstruction; BCS: Breast-conserving surgery; p: Value of significance after Poisson regression.

Table 1. Evolution of surgeries (BCS, No-BR and IBR) annually between 2012 and 2019 (number of surgeries and proportion).

Year	No-BR(n)	%	IBR (n)	%	BCS (n)	%	Total
2012	44	51.76	19	22.35	22	25.88	85
2013	49	50.00	20	20.41	29	29.59	98
2014	48	55.81	22	25.58	16	18.60	86
2015	56	47.46	30	25.42	32	27.12	118
2016	52	53.61	18	18.56	27	27.84	97
2017	40	35.40	28	24.78	45	39.82	113
2018	39	38.24	22	21.57	41	40.20	102
2019	43	40.57	22	20.75	41	38.68	106
Total p-Value	371	- p=0.299	181	- p=0.663	253	- p=0.003	805

In line with our findings, a recent Brazilian study reported an increase in breast reconstructions in Brazil between 2008 and 2014, reaching 29%, consistent with the results of this study[18]. In fact, the availability of immediate reconstruction has been related to mastectomies in some studies, especially in cases of unilateral cancer and contralateral risk-reducing mastectomy. In this sense, a retrospective study using the NCDB demonstrated that the mastectomy rate, specifically contralateral mastectomy, increased by 7% for each percentage point increase in reconstruction[11]. The rates of immediate reconstruction, on the other hand, were similar to those observed in some countries. For example, a European study evaluated 2,315 patients with early breast cancer between 2002 and 2016, in which the authors showed that the rate of immediate reconstruction was 34.3%[19]. Other factors, including barriers to access to breast reconstruction, were highlighted through a Canadian systematic review, which identified that, in rural areas, the high costs of the procedure, insufficient reimbursement by insurance companies, non-acceptance of the procedure by the patient, tumor characteristics and lack of patient awareness about reconstruction were related to non-performance of reconstruction[20].

The false impression that mastectomy could be a safer treatment may also explain the increase in mastectomies[21]. A study showed that only 38.1% of patients with unilateral breast cancer knew that contralateral prophylactic surgery had no effect on survival[22]. In fact, many patients opt for mastectomy, whether unilateral or bilateral, even after the proven observation of a reduction in ipsilateral recurrences or new contralateral tumors in patients undergoing conservative surgeries, observed over the years, possibly because of the advent of systemic therapy[23]. Another reason patients may opt for bilateral mastectomy, especially in cases of unilateral breast cancer with indication for mastectomy and reconstruction with implants, is the possibility of better symmetry: a study conducted at Memorial Sloan Kettering Cancer Center using Breast-Q in 3,489 breasts of women who opted for mastectomy with bilateral reconstruction with implants showed that the latter procedure had the best aesthetic result over a 12-year follow-up[22].

The advent of genetic counseling and multigene testing, which evaluate genes that are related to a greater hereditary predisposition for patients with unilateral breast cancer to develop recurrence or contralateral breast cancer, may also influence mastectomy rates. Recent studies conducted with thousands of patients have identified genes with a high predisposition for the incidence of breast cancer, whether first or second primary, after treatment for breast cancer, especially BRCA1 and BRCA2[24-27]. Some studies have also demonstrated a significant reduction in new tumors after bilateral mastectomy, as well as an impact on mortality in women with BRCA mutations and unilateral breast cancer[28,29]. However, in many places around the world, access to financial resources for health care is a significant impediment, as is the case for patients in the Brazilian public health system, who were the patients treated in this analysis. Furthermore, several regions of Brazil do not have the availability of cancer genetic specialists even for women with access to the private supplementary health network[30]. This issue, however, does not seem to be a problem only in countries with limited resources, with significant disparities occurring in developed countries in the management of breast cancer patients. An observational study presented at the 2023 American Society of Clinical Oncology (ASCO) meeting involving more than 1 million women who were diagnosed with any type of cancer between 2013 and 2019 assessed the prevalence of germline testing in American patients, with only 6.8% of them undergoing genetic testing, with tests performed below expectations even in cases where the test is recommended in guidelines[31]. Furthermore, patients of Asian, Hispanic or Black ethnicity had a lower proportion of tests performed[31].

Another fact that stands out in our study. is the high volume of mastectomies during this recent period. This is possibly because diagnosis still occurs in stages II and III, with great frequency, as a consequence of inadequate screening in patients in the public system. A Brazilian study conducted with 4,912 patients diagnosed with breast cancer in Brazil in 28 institutions in 2001 and 2006 demonstrated that approximately 75% of cases were stages II and III, higher than that observed in high-income countries, and approximately 80% of these cases were treated in the public system[32]. Despite this, there was paradoxically a trend towards an increase in BCS in our analysis during the study period, which may hypothetically reflect the advent of neoadjuvant therapies and a greater possibility of BCS in initially ineligible patients. In Brazil, during the study period, patients in the public system had access to adequate systemic treatment, including anti-HER2 therapy since 2013, although pertuzumab is not yet available for non-metastatic disease. Several studies have, in fact, demonstrated an increase in the rate of breast conservation and oncological safety in performing BCS in patients who were ineligible at the time of diagnosis[33,34]. The use of oncoplastic techniques frequently used in our institution may also have contributed to this trend, possibly favoring an increase in the rate of breast conservation even in extreme cases (tumors larger than 5 cm, for example), being an alternative to mastectomy[35].

Our study had some limitations, including the fact that it was a retrospective study at a single institution that treats patients in the public system, with limited resources. Therefore, our results should not be extrapolated in a generalized manner, especially in relation to institutions that treat patients with access to the private and supplementary health network in Brazil. For these patients, there is a tendency for bilateral mastectomies to increase[36], similar to what happens in some high-income countries. The analysis of a single institution may also not reflect other institutions, even public ones, or other cities or regions. Finally, factors specific to the surgical team, such as the incorporation of oncoplastic techniques and clinical-pathological characteristics of the disease, such as staging and younger age, for example, may have influenced decision-making and were not evaluated in this study[37].

To the best of our knowledge, this is the first study to assess the contemporary trend of breast surgeries (mastectomy and BCS) for the treatment of early breast cancer in an institution with limited resources — in this case, in Brazil. These data reveal the importance of discussion, as well as public policies for the incorporation of new technologies, including genetic testing. As in other places in the world, access and disparity are relevant problems in Brazil, whether for surgical treatment, including immediate reconstruction, or even for the incorporation of new drugs with high costs for systemic treatment.

CONCLUSIONS

We did not see an increase in mastectomy rates during the study period (2012–2019) in a public institution with limited resources. However, a trend of increasing BCS rates was demonstrated over the years at HGF. Although these results may not be generalizable, suggest that rising mastectomy trends may not be consistent across countries, especially with differences in access to health care systems, and warrant further studies and discussion on this scenario.

AUTHORS' CONTRIBUTION

FPC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TMGP: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FPZ: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. ECM: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Conceptualization, Vali dation, Visualization, Writing – original draft, Writing – review & editing. MA: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. FPB: Conceptualization, V alidation, Visualization, Writing – original draft, Writing – review & editing. GGN: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. ALF: Conceptualizat ion, Validation, Visualization, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
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Photobiomodulation for the Prevention of Chemotherapy-Induced Peripheral Neuropathy: Randomized Clinical Trial Protocol

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ABSTRACT

Introduction: Chemotherapy applied as a breast cancer treatment may result in chemotherapy-induced peripheral neuropathy (CIPN) as a side effect, encompassing varying degrees of toxicity, according to the employed drug's pharmacokinetics, administration period, and cumulative dose. In this sense, photobiomodulation employing LASER or LED comprises a safe and non-pharmacological low-cost resource that has been widely studied for the mitigation and even resolution of various oncological comorbidities. The objective of this study is to evaluate the effectiveness of photobiomodulation employing a LED Therapeutic Display (LTD) in the prevention of lower limb CIPN in breast cancer female patients undergoing chemotherapy. **Methods:** This study encompasses a randomized double-blind superiority clinical trial including women aged 18 and over presenting breast cancer stages I to IIIC with indication for curative treatment applying neoadjuvant or adjuvant chemotherapy. Following recruitment, patients will be allocated into three groups: two intervention groups, which will undergo infrared and red LTD (A) and infrared, red, and violet LTD (B), and a control group (C), which will apply LTD with no light emission. The LTD applications will be conducted at home for 20 minutes daily on each plantar region, until the last day of chemotherapy. All groups will be assessed at the beginning of the chemotherapy treatment, during each cycle, and at the end of the treatment (at 30 days, 3 and 6 months). Lower limb CIPN incidence, pain, body balance, sensitivity, and quality of life will be evaluated, as well as LTD use satisfaction, treatment adherence, and CIPN impacts on daily living activities. **Results:** This study will evaluate the effectiveness of photobiomodulation employing LTD in preventing lower limb CIPN in Brazilian breast cancer female patients undergoing neoadjuvant or adjuvant chemotherapy. The results will encompass quantitative and self-reported patient data. **Conclusions:** This study is expected to demonstrate a new prevention modality for this breast cancer treatment complication.

KEYWORDS: breast cancer; peripheral nerve repair; photobiomodulation therapy.

INTRODUCTION

Breast cancer is the most common malignancy among women in Brazil, except for non-melanoma skin tumors[1]. Despite technological advances, adverse cancer treatment effects and chronic toxicities are still a challenge for healthcare teams[2].

Systemic therapy contributes to overall and disease-free survival based on the control of micrometastases presenting dissemination potential[3]. Chemotherapy involves administering antitumor chemical agents, either neoadjuvantly and/or adjuvantly. Neoadjuvant chemotherapy aims to reduce tumors to allow viable mastectomies and/or enable conservative surgeries. It is currently applied in early and locally advanced breast cancer cases, reducing the cancer stage and determining tumor responses to therapy. Adjuvant chemotherapy, on the other hand, aims at controlling remaining disease cells, lowering recurrence rates and improving long-term survival rates[4].

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Some known adverse chemotherapy effects include emotional, social, and self-esteem changes, functional loss, nausea, vomiting, fatigue, alopecia, mucositis, skin changes, and complications such as infections, peripheral neuropathy, febrile neutropenia, renal, hepatic, and cardiac toxicity[5].

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common chemotherapy side effects and appears progressively during the chemotherapy. This condition is generally described as a bilateral and distal symmetric axonopathy generated by a drop in action potential amplitude and an increase in distal latency caused by deterioration of the peripheral nervous system, resulting in neural degeneration. CIPN can distort and/or interrupt reciprocal information from the central nervous system and the extremities of the body, often generating painful stimuli. The dorsal root ganglion, which plays an important role in the transmission of sensory signals, appears to be the main neural injury site, resulting in decreased cellular metabolism and axonal transport[6,7].

Motor symptoms typically manifest as distal weakness in the feet and hands, gait and balance disorders, and fine movement (writing, buttoning clothes, cutting, and sewing) difficulties. Sensory symptoms are represented as bilateral paresthesia, frequently reported as numbness, allodynia, neuropathic pain, and tingling in 90% of CIPN. Furthermore, a sensation of "wearing a thin sock or glove" is also common, as well as difficulty "holding things" and discriminating shapes, textures, and/or temperatures. These manifestations generally occur at the beginning of chemotherapy, between the first and third cycle, with peak severity occurring around the third month, leading to treatment delays due to pauses that might become necessary for tissue recomposition[7].

Some factors influence the incidence of CIPN, such as patient age, dose intensity, cumulative dose, chemotherapy duration, the co-administration of other neurotoxic chemotherapy agents, and pre-existing conditions, such as diabetes and alcohol consumption[8].

The ideal CIPN treatment, currently focused on controlling symptoms, has not yet been fully elucidated. In this sense, photobiomodulation employing low-power lasers is a safe, non-pharmacological, and low-cost resource that has been widely assessed for the mitigation or even resolution of various oncological comorbidities, and its use in CIPN cases has increased exponentially[9].

The light emission produced by a light emitting diode (LED) is a form of photobiomodulation, acting on capillary permeability and the synthesis of adenosine triphosphate in mitochondrial cells and of proteins such as collagen and elastin. LED devices can be used at wavelengths ranging from 405 nm to 940 nm. Biological responses to phototherapy, such as increased local blood circulation, cell proliferation stimulation, increased collagen and elastin synthesis, and adenosine triphosphate cellular energy modulation, are mainly affected by wavelength, providing an optional therapeutic resource to conventional treatments[10]. It is important to note that the use of LED-based devices is also beneficial concerning outpatient economy, as these equipments consume low amounts of energy and comprise lower-cost materials compared to light amplification by stimulated emission of radiation (LASER)[10].

The effectiveness of photobiomodulation employing LASER and/or LED therapy is also recognized as an effective intervention in breast cancer female patient cases for other clinical conditions such as dysgeusia, oral mucositis, lymphedema, and radiotherapy-induced dermatitis[11-13]. However, few clinical trials evaluating the effectiveness of photobiomodulation in preventing and treating CIPN are available to date[14]. The therapeutic pain control effect seems to be based on the mitochondrial mechanism of action, as described above, but also on the interaction of photonic energy with calcium ion pumps and cell membrane permeability modulation, allowing the balance of sodium and potassium ions across the cell membrane to rebalance the sodium-potassium pump[15-17]. Joy et al.[2] described a randomized pilot study evaluating photobiomodulation effectiveness in preventing breast cancer patient CIPN. The patients were divided into a control group (n=16) and an intervention group (n=16), receiving photobiomodulation applications twice a week during the entire chemotherapy treatment employing a LASER at two different wavelengths, 905 nm and 808 nm, at 4 J/cm^2. The authors concluded that patients in the intervention group demonstrated promising results in preventing symptoms related to peripheral neuropathy. Numbness in the extremities of the upper and lower limbs worsened significantly ($p<0.001$) in the control group, and a better quality of life was determined in the intervention group[2].

In this context, evaluating the effectiveness of photobiomodulation by employing LED Therapeutic Display (LTD) in preventing CIPN is paramount for the development of strategies that facilitate breast cancer control and its consequences within a Public Health System scope, comprising a low-cost and safe therapeutic proposal with significant clinical applicability.

Explanation for the choice of comparators

The participants in the control group (C) will receive the LED without light emission, capable of emitting the same audible alarms as the LED used in the intervention groups. In the first intervention group (A), red light and infrared LEDs will be applied, and in the second group (B), red, infrared, and violet light LEDs will be used. The three groups are necessary to obtain more reliable results and better understand the effects of different combinations of lights on preventing neuropathy, allowing us to compare the results with the control group, verifying whether the changes found in the other groups are actually due to the emitted lights or if they could occur due to other factors. When comparing groups A and B, we hope that the addition of violet light may provide complementary benefits or a greater enhancement to the effects of red and infrared light.

Research hypotheses

This study protocol describes a randomized superiority clinical trial encompassing breast cancer female patients undergoing chemotherapy in which the application of photobiomodulation through LTD in intervention groups A (red light and infrared LTD) and B (red light, infrared, and violet LTD) will be compared to a control group C (placebo). The study hypothesis is that the LTD applied to intervention groups A and B from the first day of chemotherapy is effective in preventing CIPN symptoms. The second hypothesis is that CIPN may be associated with worsening symptoms, such as pain, body balance, sensitivity, and quality of life.

Study objectives

Primary objective

The primary objective of the study is to evaluate the effectiveness of photobiomodulation employing LTD in preventing lower limb CIPN in breast cancer female patients undergoing chemotherapy at the National Cancer Institute, Cancer Hospital III (HCIII/INCA) – Brazil.

Secondary objectives

The secondary objectives of the study consist of evaluating:

- The incidence and clinical characteristics of lower limb CIPN after beginning chemotherapy according to the intervention group;
- Photobiomodulation effectiveness employing LTD in preventing lower limb CIPN;
- Photobiomodulation influences employing LTD on pain symptoms, body balance, and sensitivity, according to the intervention group;
- Health-related quality of life before and after chemotherapy and the presentation/development of neurotoxicity symptoms, according to intervention group;
- Photobiomodulation satisfaction and the impact of CIPN on daily living activities during chemotherapy.

Study design

This study comprises a randomized superiority clinical trial with three arms—two intervention groups and one control group—carried out in a reference breast cancer treatment center.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Patients and study location

This study will be carried out at HCIII/INCA, in the city of Rio de Janeiro, Brazil, encompassing breast cancer female patients with indication for neoadjuvant or adjuvant chemotherapy.

Eligibility criteria

Women aged 18 or over presenting stage I to IIIC breast cancer with indication for curative treatment employing neoadjuvant or adjuvant chemotherapy at the HCIII/INCA will be included in this study.

Patients with a previous diagnosis of other primary cancers, who underwent surgery and/or chemotherapy to treat breast cancer at another institution, with previous feet sensation alterations, without the ability to respond to questionnaires, and unable to receive photobiomodulation due to acute lower limb infection will be excluded.

Treatment protocol/interventions

All patients will be evaluated by a physiotherapist, subjected to the first LTD application session and instructed to continue with the application at home from the first day of chemotherapy. All patients will receive a booklet with instructions for the correct use of the LTD and will be instructed to fill out an application frequency diary and continue with their usual physical activities.

The LTD applications must be carried out daily for 20 minutes on each extremity (soles of the feet), until the last chemotherapy treatment day.

Tissue from the extremities of the lower limbs will contact the LTD during its application in order to ensure uniform photobiomodulation administration (Figure 1).

Group A: Intervention group employing an LED red light (RL) and infrared (IR) board. Sequential LED treatments will be administered through a Sportllux Ultra LTD (Cosmedical) applying a predefined cycle, with a combination of light emitters at two wavelengths, namely 42 RL LED diodes (660 nm) and 42 IR LED diodes (850 nm); LTD measuring 10 x 12 cm; average power of each LED RL: 28.5 mW/cm^2 and IR: 23 mW/cm^2; operating mode: continuous; polarization: random; power density: 18.025 mW/cm^2; opening diameter of each LED: 1 cm^2; application time: 20 minutes; energy RL: 34.2 J/cm^2 and IR: 27.6 J/cm^2.

Group B: Intervention group with a red light, infrared, and violet LTD. Sequential LED treatments will be administered through a Sportllux Ultra LTD (Cosmedical) applying a predefined cycle, with the combination of light emitters at three wavelengths, namely 18 red light LED diodes (660 nm), 18 infrared LED diodes (850 nm), and 36 Violet LED diodes (420 nm); LTD measuring 10x12 cm; average power of each LED RL: 28.5 mW/cm^2, IR: 23 mW/cm^2, and Violet 52 mW/cm^2; operating mode: continuous; polarization: random; power density: 23.325 mW/cm^2; opening diameter of each LED: 1 cm^2; application time: 20 minutes; energy RL: 34.2 J/cm^2, IR: 27.6 J/cm^2, and Violet 62.4 J/cm^2.

Group C: Control group using an LTD with no light emission, using a Sportllux Ultra LTD (Cosmedical); LTD measuring 10 x 12 cm, and application time of 20 minutes.

Figure 1. LED Therapeutic Display used on lower limbs (on the soles of the feet) and application method.

Criteria for discontinuing or modifying the allocated interventions

The treatment will be suspended in case patients complain of sensory changes or pain in the CIPN-affected region following the LTD application. In the event of any other unforeseen changes, the healthcare team will assess the patients, and the necessary procedures will be adopted.

Strategies to improve adherence to interventions

Aiming at improving adherence to treatment, participants will receive a frequency diary to inform the dates they apply the LTD daily and whether it is being done to both feet for 20 minutes. This will be reassessed with each new chemotherapy cycle.

Relevant permitted or prohibited concomitant care during the trial

It is important to highlight that any other intervention by CIPN prevention study participants will not be permitted. Patients must carry out their normal routines, and the only interference in this study will be the application of the provided LTD.

Outcomes

First outcome

CIPN will be assessed by the Chemotherapy Induced Peripheral Neuropathy Assessment Tool (CIPNAT), at the beginning of chemotherapy, at each new cycle, and at 30 days, 3 and 6 months after the end of treatment. It contains 36 scored items in total, which evaluate the occurrence of symptoms, severity, distress, and frequency of peripheral neuropathy symptoms (sensitivity to cold, muscle and joint pain, numbness and tingling of hands and feet, loss of balance, weakness, and nerve pain), 14 items that assess interference with usual daily activities, ending with an open question about injuries resulting from the presence of symptoms. Patients will be asked about the development of each symptom since the beginning of chemotherapy. "No" responses receive a score of 0 and "yes" receive a score of 1 (score range 0–9). For each "yes" response, participants will answer additional items evaluating the severity, distress, and frequency of each reported symptom, employing a numerical scale from 0–10. Combining these three factors results in a total score range 0–270, with higher values indicating greater severity, distress, and frequency of the symptoms. The score for the group of symptom items experienced with added occurrences can range from 0–279. Higher scores on the symptom scale correspond to higher CIPN grades. Nineteen of the items are not scored in the CIPNAT, as they are described with the aim of obtaining information about the specific anatomical location of certain symptoms, the time of day when they occur most severely, and when the symptoms are most severe after the chemotherapy protocol. This questionnaire has been translated and validated into Brazilian Portuguese[18].

Second outcome

Secondary outcomes will be assessed before the beginning of chemotherapy, and at 30 days, 3 and 6 months after the end of treatment, as follows:

Pain: will be assessed using the short-form McGill Pain Questionnaire (SF-MPQ). This instrument initially asks patients about the presence of pain in the last seven days and, if so, its location. From there, sensory (1–11) and affective (12–15) pain characteristics are evaluated on a scale from 0–3 (absent, mild, moderate, and intense). A Visual Numerical Scale (VNS), in which the patient scores a pain intensity from 0–10, is also a part of the instrument. Finally, the patient is encouraged to identify his/her entire pain experience on a scale of 0–5 (no pain, minimal, uncomfortable, painful, horrible, excruciating). In the end, five scores are obtained: sensitive/sensory pain index (0–33 points), affective pain index (0–12 points), total index (sum of sensory and affective pain indexes), intensity of pain (0–5 points), and assessment of the entire pain experience (0–5 points). The final assessment will be calculated based on the frequency of patients who are sensitive and who present affective pain, pain intensity, and miscellaneous subgroups[19].

Body balance: the Timed Up and Go Test (TUG) aims to assess functional mobility and dynamic balance, scoring the risk

of falls when getting up, walking, turning, and sitting. Subjects sitting in a chair will be asked to get up and walk to a point on the floor, turn around and sit down in the chair again, and the time they complete this journey will be timed. Times of less than 10 seconds suggest individuals with mobility classified as normal; subjects with times between 10 and 19 seconds have good mobility, and patients who take 20 to 29 seconds are classified as regular mobility. Times of 30 seconds or more tend to reflect subjects with impaired mobility. Patients will be shown what the test consists of in advance and instructed to walk at their usual pace and speed. In case of doubt, the test will be repeated. For safety reasons, the examiner will walk alongside the patients during the test[20].

Sensitivity: will be assessed using an Esthesiometer (monofilaments). Patients will be evaluated in the supine position in a quiet and comfortable environment with as minimal interference as possible. The test will be demonstrated previously using a skin area with normal sensitivity; patients will be instructed to close their eyes; 10 points will be tested bilaterally on the lower limbs, totaling 20 points corresponding to the paths of the tibial, sural, saphenous, and deep peroneal nerves[21]. This technique is evaluated as described by Bell-Krotoski[22].

Health-related quality of life: a Brazilian Portuguese version of Functional Questionnaire Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX) will be used. This instrument evaluates recent situations, referring to quality of life and neurotoxicity symptoms, totaling 38 questions divided into five subscales: a) Physical Well-being (7 questions; maximum score of 28 points); b) Social/Family Well-being (7 questions; maximum score of 28 points); c) Emotional Well-being (6 questions; maximum score of 24 points); d) Functional Well-being (7 questions; maximum score of 28 points); and Neurotoxicity Symptoms (11 questions; maximum score of 44 points). In this assessment, the interviewee is asked about recent information about their quality of life, functionality, and symptoms. If the answer is affirmative, meaning the item is a reality in their lives, they are asked to rate the intensity on a scale of 1–4. A total score is then obtained for each subscale and indices, indicating the relationship between them. The higher the score on each subscale and/or established indices, the better the patient's quality of life[23].

Satisfaction with the use of photobiomodulation: questions will be asked based on a semi-structured questionnaire about overall satisfaction and difficulty using the LTD, which will be classified as: I don't know how to answer, little, medium or very satisfied. Regarding changes in social life due to using the LTD, it will be classified as: no change, improvement, or worsening in social life. Changes at the application site such as pain, burning, discomfort, redness, itching, or the need to interrupt treatment, will be classified according to the Visual Analogue Scale (VAS), and the presence or absence of these symptoms.

Treatment adherence: will be checked using the LTD application diary, to be completed daily during the treatment period. In this diary, patients must inform the date of the LTD application, whether it was performed on both feet, and whether it lasted 20 minutes on each limb. The LTD application diary must be delivered on the last day of chemotherapy treatment.

Impact of peripheral neuropathy on activities of daily living: assessed using the CIPNAT. The participant who reports the presence of one or more symptoms in the assessment of the nine specific previously questioned neuropathic symptoms will be assessed by 14 items on the interference of these symptoms in daily activities. Interference in each activity is measured on a numerical scale from 0–10. The score in this set can range from 0–140, in which a high score indicates significant interference with activities due to neuropathic symptoms[18].

Patient monitoring

Patients will be evaluated in person at each new chemotherapy cycle and at 30 days, 3 and 6 months after the end of treatment. These reassessments will not bring any financial burden to patients as they will be carried out on the days and times during routine appointments.

Sample size

To calculate the sample size, with 80% power to detect a difference between groups of 1.1 for CIPN, considering a significance level of 5% and a loss percentage of 15%, in a one-tailed hypothesis test, a sample of 186 patients (62 per group) is required.

Recruitment

All patients who attend HCIII/INCA for their first chemotherapy consultation will be recruited to assess the study's eligibility criteria. Patients considered eligible will be informed about the objectives, treatment groups, adverse effects, and non-obligation to participate in the study. After agreeing to participate, they will be invited to sign an informed consent form, undergo an interview and physical assessment, and be randomized into the intervention or control groups. All patients will be evaluated and guided by the nursing team regarding skin care and symptom control before starting chemotherapy, according to the institutional routine. The study inclusion period will occur from March/2023 to June/2024 (Figure 2).

METHODS: INTERVENTION ALLOCATIONS (FOR CONTROLLED TRIALS)

Randomization

After recruitment, patients will be allocated into three groups: two intervention groups and a control group. The randomization will be carried out in a 1:1 allocation ratio for the three groups

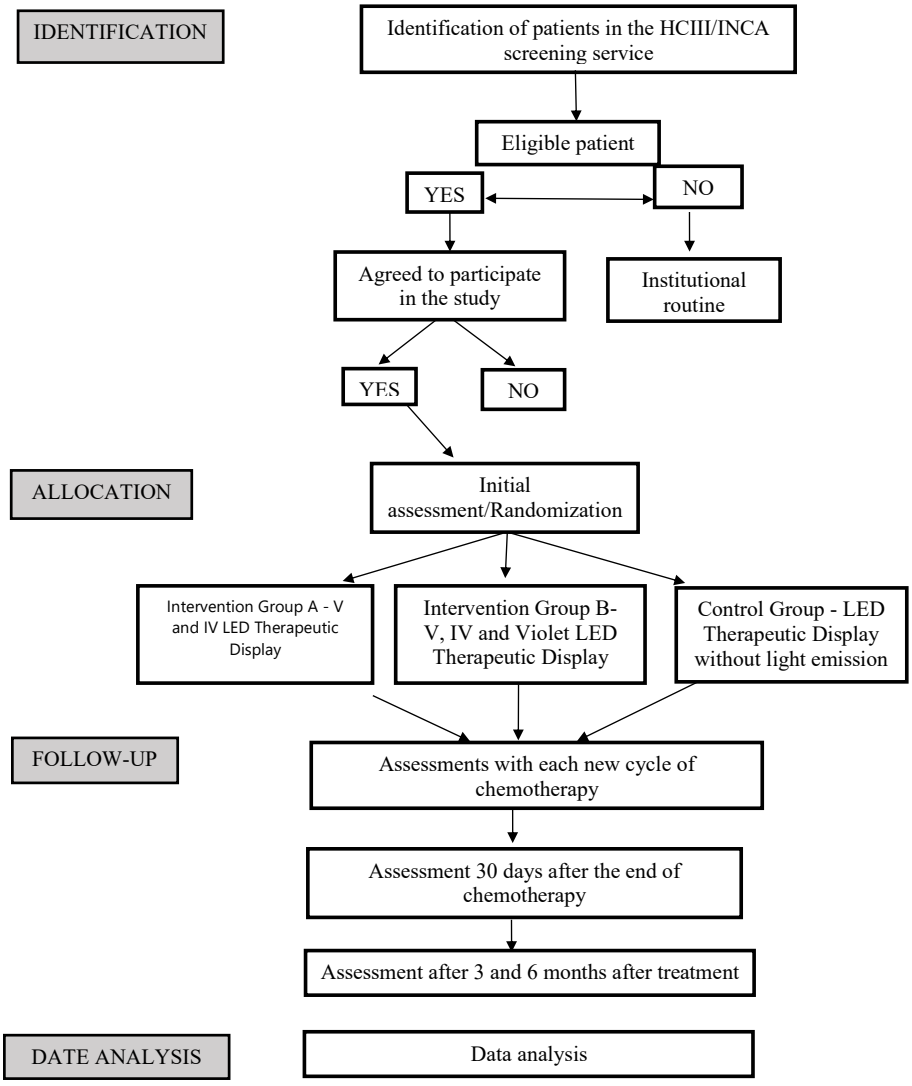

Figure 2. Recruitment and assessment flowchart. Infrared (IR) and Red (V) LED Therapeutic Display, and Infrared, Red and Violet (Sportllux Ultra Model) light. Placebo comparator: use of a LED Therapeutic Display with no light emission (modified Sportllux Model).

for every 15 patients, generated by a block of sealed and opaque envelopes with the following allocation codes: five codes for intervention group A, five codes for intervention group B, and five codes for control group C. Patients will be instructed on the use of the LTD and monitored during the chemotherapy period and up to 6 months after the end of treatment. All assessments, interventions, and data collection will be carried out by professionals trained and qualified for this purpose.

Blinding

Due to the nature of the intervention, physiotherapists supervising the application of the photobiomodulation technique will not be blinded. Only outcome assessors and patients will be blinded to group allocation.

To avoid a breach of anonymity, patients will be identified by a code and not by name or other form. Only the main researcher will have access to these codes and will assume responsibility for data confidentiality. All results will be presented together, consequently, no case can be recognized individually.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection

Data collection will be carried out by the study researchers through questionnaires, physical examinations, and clinical information collection from physical and electronic medical records, and stored in instruments suitable for research.

Variables regarding sociodemographic, clinical characteristics, lifestyle habits, tumor, and treatment characteristics will also be obtained from physical and electronic records.

Plans to promote patient retention and comprehensive follow-up

Participants will receive the necessary information at the time of recruitment to understand how the assessments will be performed and the importance of committing to complete the follow-up, including reassessments at each new chemotherapy cycle, and at 30 days, 3 months, and finally 6 months after the end of treatment. Any study participant may withdraw from the study at any time, without necessarily explaining the reasons. Patients will be monitored via telephone so that they may attend the physiotherapy department for assessment.

Descriptive and control variables

Variables related to the patient's characteristics will be used (age, skin color, marital status, education, occupation, and tobacco consumption), as well as clinical data (dominant side, independence in personal care, carrying out domestic activities, self-assessment of global health status, and comorbidities), condition of the skin of the feet (hyperemia, heat, wound, and edema), and tumor and oncological treatment characteristics (clinical staging, neoadjuvant or adjuvant treatment, histological type and grade, HER2, estrogen receptor, progesterone receptor, Ki67 receptor, date, side of surgery, type of breast surgery, breast reconstruction, axillary approach: sentinel lymph node biopsy, and/or axillary lymphadenectomy, number of removed and compromised lymph nodes, histopathological staging, chemotherapy, radiotherapy, hormone therapy and use of target therapy).

Data management

The data will be managed by physiotherapists who will fill out the information on sheets of paper. These will be kept in a safe place for a period of up to five years, in case of need for review or request by the Research Ethics Committee. The responsibility for filling in data in the electronic spreadsheet will rest with the same initial collectors. All data from the electronic bank will be reviewed and compared with paper forms before exporting to the program in which the analyses will be conducted, namely Statistical Package for Social Science (SPSS).

Data analysis

Statistical analyses will be conducted following the intention-to-treat principles.

Data normality will be examined using the Kolmogorov-Smirnov test, considering variables presenting $p>0.05$ as normal distribution. Descriptive analyses will be performed of the baseline characteristics for each group (A, B, and C). For continuous variables, central tendency and dispersion measurements will be carried out. The differences in means between groups for continuous variables with normal distributions will be compared using the independent samples T-test, while with non-normal distributions, the Mann-Whitney U test will be performed. Categorical variables will be described by relative and absolute frequency distributions and compared between groups through the chi-square test or Fisher's exact test, according to the number of individuals in the different categories of the analyzed variable.

Generalized linear models will be conducted, comprising tests based on longitudinal studies, based on a linear regression model of repeated measures between the three groups. The objective is to evaluate the association between photobiomodulation employing LTD and time (at the end of each chemotherapy cycle, and at 30 days, 3 and 6 months after the end of treatment) and the prevention of lower-limb CIPN, as well as the interaction between groups and time, in addition to their respective 95% confidence intervals.

The incidence of CIPN will be described by the cumulative incidence in all groups and within each group by a survival analysis using the life table method (at fixed times, namely at the end of each chemotherapy cycle and at the end of treatment). A subgroup analysis will be carried out with strong biological rationality and potential interaction effects. For subgroup C (control), quality of life will be compared through the FACT/GOG-NTX questionnaire before and after chemotherapy. We will also verify whether the effects of the placebo treatment interfere with the quality of life of these patients. All analyses will be carried out using the SPSS, version 20.0.

METHODS: MONITORING

Data monitoring

A data monitoring committee was not informed for this study. Therefore, research physiotherapists will conduct controls and notifications and assess possible adverse effects and symptoms that may be reported by patients. If adverse effects resulting from the intervention administered are observed, the participant may withdraw from the study, following an institutional routine where all necessary technical support will be applied.

Risks and benefits

Carrying out physical assessments may pose risks, although minimal, of possible sensory changes or pain when palpating the region affected by CIPN and some discomfort due to the pressure caused by the LTD application. Patients will be constantly monitored through in-person assessments and telephone contact, as, despite the low risks, allergic reactions such as skin irritation, itching, redness, minimal local superficial heat, and discomfort due to the pressure of the material on the skin during treatment may occur. If this does happen, patients will be referred for medical evaluations at the institution's emergency department.

Patients will not be remunerated for their participation, and this research may or may not offer direct patient benefits. By agreeing to the use of their information and/or material in

the manner described above, patients will be informed that they will not have any benefits or financial rights over any results from this research. The main benefit of participation will be that, in the future, the results achieved in this research may lead to a diagnosis and treatment for this type of alteration and benefit other patients. This research may or may not offer direct benefits to patients, as it is a study that is still in progress, so the following are expected as possible and potential benefits, according to current literature: CIPN prevention, pain improvement, functionality, and quality of life, enabling planning for actions to control complications.

Audit

No audits were planned or commissioned for this study.

ETHICS AND DISCLOSURE

Ethics

This study was approved on November 3, 2022, by the Ethics and Research Committee of the National Cancer Institute (CEP/INCA) under No. 5,737,539, in accordance with the attributions defined in CNS Resolution No. 466/2012 and CNS Operational Standard No. 001/2013.

This clinical trial is registered at ClinicalTrials.gov under the identifier NCT05663723.

Protocol changes

Any protocol modifications that may impact this study's conduct, potential patient benefits, or affect patient safety, including changes to the objectives, study design, population, sample sizes, and study procedures, as well as to significant administrative aspects, will require a formal amendment to the protocol. Such changes will be agreed by the authors and approved by the Ethics and Research Committee of the National Cancer Institute (CEP/INCA) before implementation and notified to the health authorities following local regulations.

Any administrative protocol changes that do not affect how the study will be conducted will be agreed to by the authors and documented in a memo. The Ethics Committee/CEP may be notified of administrative changes at the author's discretion.

Consent

Item not applicable, as this manuscript does not contain individual information or personal study participant data.

Confidentiality

The patients will be interviewed individually by trained professionals, in a calm environment, respecting established ethical-legal precepts, so that they feel comfortable answering the questionnaires. The collected data will be confidential and used without identification, where only the main researcher or some study researchers will have authorized access for use.

Disclosure Plan

This study protocol aims to answer whether the use of photobiomodulation is effective in preventing CIPN in breast cancer female patients. The results of this research will be published in scientific publications, at national and international events, and on other media portals. The study protocol will be presented to healthcare professionals and shared with patient groups through workshops and webinars.

Financing

The scientific expenses related to the publication and the Sportllux Ultra and modified Sportllux model LTD were covered by the company Bled Med Comércio e Distribuição Limitada (São Paulo, Brazil) through sponsorship and material donation. The remaining expenses are being covered by the researchers responsible for the study.

The authors declare that they have not received any financial support that could influence the content of this article. The principal investigators have no financial interest in conducting this study. This investigation was supported by the HCIII/INCA. The authors' interest is strictly for academic purposes.

Anke Bergmann receives Research Productivity grants financed by the Brazilian National Council for Scientific and Technological Development (CNPQ).

Declaration of interest

The authors declare that they do not receive any financial support that could influence the contents of this article. The principal investigators have no financial interest in conducting this study.

Data availability

No data was used for the research described in this article.

Auxiliary and experimental post-care

If an increase of over 10% is observed in adverse effects resulting from the interventions after the start of chemotherapy and patient inclusion in the study, the patient will be removed from the research and directed to continue the standard treatment offered at the Institution as per routine.

RESULTS

The results of this study will provide data based on quantitative, qualitative, and self reported responses from participants.

After analyzing the data, positive results are expected in the prevention of neurotoxic symptoms. This is the first study to evaluate CIPN prevention using LTD as an intervention. Planned follow-up will allow for short- and long-term data observations.

DISCUSSION

This study will evaluate the prevention of CIPN in Brazilian women with breast cancer through photobiomodulation using LTD, comparing red light and infrared LTD (group A), red light, infrared and violet LTD (group B), and LTD with no light emission (group C).

CONCLUSIONS

This study is expected to demonstrate a new prevention modality for this breast cancer treatment complication.

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AUTHORS' CONTRIBUTIONS

MCF: Conceptualization, Investigation, Writing – original draft, Validation, Writing – review & editing. EANF: Conceptualization, Validation, Writing – original draft, Writing – review & editing. RMC: Conceptualization, Validation, Writing – original draft, Writing – review & editing. DMT: Conceptualization, Validation, Writing – original draft, Writing – review & editing. SSA: Conceptualization, Validation, Writing – original draft, Writing – review & editing. JL: Conceptualization, Validation, Writing – original draft, Writing – review & editing. RRA: Conceptualization, Validation, Writing – original draft, Writing – review & editing. AB: Conceptualization, Validation, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
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Oxybutynin use as a hot flash reducer in breast cancer survivors in the use of tamoxifen: a pilot randomized clinical trial

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ABSTRACT

Introduction: Breast cancer is a heterogeneous disease in which genetic and environmental factors are involved. The most prevalent types are those expressing hormone receptors, consisting of 60% to 70% of all cases in developed countries. Therefore, the most common type of therapeutic approach is hormone therapy. Estrogen blockers, such as tamoxifen, and aromatase inhibitors, such as anastrozole, are the most prescribed medicines for these types of cancer. The purpose of this article was to assess the effects of once-daily oxybutynin 5 mg on frequency and severity of hot flashes in women with breast cancer using tamoxifen. **Methods:** A two-month double-blind, placebo-controlled, pilot randomized clinical trial in women with breast cancer using tamoxifen that were experiencing hot flashes. These women were treated daily with oxybutynin 5 mg (n=11) or a placebo (n=12). The co-primary outcome was to reduce, from baseline to month two, the frequency and severity of hot flashes symptoms. **Results:** Reductions in both frequency and severity of hot flashes were observed in women who received oxybutynin 5 mg/day compared to placebo, even though it was not statistically significant. Adverse effects reported by the oxybutynin arm were tachycardia and decrease in appetite (9.1%), and in the placebo arm were headaches (8.3%), xerostomia (16.6%), diarrhea (8.3%), and dry skin (8.3%). **Conclusions:** oxybutynin is a safe nonhormonal therapy for hot flashes in women with breast cancer using tamoxifen.

KEYWORDS: oxybutynin; breast cancer; tamoxifen; hot flashes.

INTRODUCTION

Breast cancer (BC) is a heterogeneous disease in which genetic and environmental factors are involved[1]. BC is a common cancer among women worldwide, and based on molecular and histological analysis, it should be divided into three groups: (i) estrogen receptor (ER^+) or progesterone receptor (PR^+) BC; (ii) human epidermal receptor 2 ($HER2^+$) BC; and (iii) triple negative (ER^-, PR^- $HER2^-$) BC. The classification is important since the treatment approaches are based in BC molecular characteristics[2,3]. The most prevalent types of BC are the ones expressing hormone receptors (HR), consisting of 60% to 70% of all BC cases in developed countries. Therefore, the most common type of therapeutic approach is hormone therapy[4]. Estrogen blocker, such as tamoxifen, and aromatase inhibitors, such as anastrozole, are the most prescribed medicines for these types of cancer[5].

Tamoxifen (TAM) is a selective estrogen receptor modulator regularly used in routine clinical practice for almost 40 years. This drug competes with estrogen for binding to the ER in BC that express ER[6,7]. Five years of adjuvant TAM therapy reduce BC recurrence risk by almost one half, with further long-term survival after ten years of treatment[8,9]. Although TAM is generally well-tolerated for pre- and perimenopausal women, hot flashes (HF), as other vasomotor side effects, can be a problematic toxicity for up to 78.0% of women in the long term[10,11]. Some studies have suggested that HF are an indicator of clinical effects[12-14], and Baxter et al.[15] showed an inverse relationship between endoxifen levels and HF severity.

Oxybutynin is an anticholinergic drug used to treat urinary frequency, incontinence, and overactive bladder[16]. A retrospective study suggested that oxybutynin could be used for women with refractory HF[17]. A previous clinical trial stablished that

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oxybutynin could be a well-tolerated drug option for women to treat HF with or without BC[18], even though anticholinergic medications can induce atropine-like symptoms, such as dry mouth, constipation, drowsiness, and blurred vision[19].

Therefore, the aim of this present study was to compare oxybutynin at a low dose of 5 mg once a day with placebo in treating HF with minimum adverse effects.

METHODS

Study design and participants

This was a randomized, prospective, double-blinded, placebo-controlled pilot clinical trial conducted at Hospital Regional de Presidente Prudente (HRPP), São Paulo state, Brazil. Eligible patients were adult women with BC history, treated in the HRPP, in use of TAM, regardless of the type of cancer treatment they had. TAM dose should be stable for at least 28 days, and treatment should continue during all the study period. $HER2^{+}$-directed therapy was allowed. Exclusion criteria were prior use of oxybutynin or contraindications to oxybutynin.

Written informed consent was obtained from each participant, and the study protocol was reviewed and approved by the Research Ethics Committee of the HRPP and the Universidade do Oeste Paulista, under the CAAE 38839420.3.0000.5515.

Random assignment and masking

Women were randomly assigned to receive either 5 mg/day of the oxybutynin oral tablet formulation or a placebo, resulting in a 1:1 chance of receiving one or the other. The oxybutynin or placebo formulations were secretly prepared by a pharmacist who did not participate directly in the study. Web-based randomization was used, following the Pocock and Simon's dynamic allocation procedures[20]. Stratification factors included age, sex, cancer staging, treatment, HF duration, and HF frequency per day.

Procedures

During the first week of the study, treatment was assigned to groups, and a questionnaire was completed to establish baseline symptoms. The questionnaire Research Questionnaire for Breast Cancer Patients in use of Tamoxifen consists of 11 items that assess personal information, number of HF per day, intensity of HF, and side effects of oxybutynin such as xerostomia, headache, diarrhea, dysuria, and abdominal pain. These data were reassessed after 60 days of follow-up through telephone calls.

Outcomes

The primary outcome was the intrapatient reduction of the number and intensity of HF events, being the intensity assumed as grade 1 = mild; grade 2 = moderate; grade 3 = severe; and grade 4 = very severe. The secondary outcome included 2-month follow-up to evaluate the adverse effects of oxybutynin.

Statistical analysis

Applying a two-sided 5% significance level, 40 patients were designated for the study, from January to April 2021. After evaluation of eligibility, 27 patients were randomly allocated for the oxybutynin or placebo group (outlined in Figure 1). Categorical variables were expressed as proportions and continuous variables as means ± standard deviation. The groups were compared using chi-square (χ^2) test, and oxybutynin doses were compared against placebo applying the Fisher's exact test. Additionally, a logistic regression model was employed, and a statistical significance was defined as a p-value less than 0.05 ($p<0.05$). All statistical analyses were performed using GraphPad Prism version 9.0.0 (GraphPad Software, Boston, MA, 2020).

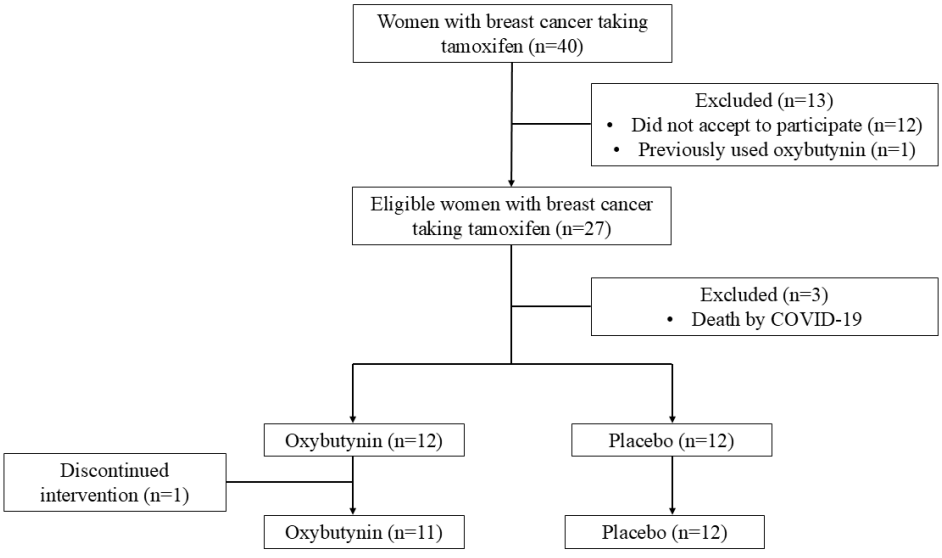


Figure 1. Study flow chart.

RESULTS

Baseline characteristics of the total cohort

In the present study, 40 patients who underwent BC treatment and were on TAM use between January and April 2021 were enrolled. After applying the inclusion and exclusion criteria, 27 patients were eligible for the study. Unfortunately, three patients died of COVID-19; therefore, 24 cases were randomly assigned (1:1) to oxybutynin or placebo treatment arm. Subsequent to this enrollment, one patient allocated in the oxybutynin treatment arm discontinued the intervention.

A statistical difference was found between the mean age in the oxybutynin and placebo groups. Meanwhile, all other baseline characteristics were well balanced, such as the proportion of postmenopausal state, ethnicity, tumor, node, and metastasis (TNM) status, and HF intensity. Table 1 describes the baseline characteristics of all patients.

Hot flashes reduction and adverse effects

HF scores and intensity reduction are presented in Table 2 and Figure 2. Patients on each arm, oxybutynin and placebo, achieved reductions in HF scores, being 60.3% and 33.4%, respectively. However, this difference was not statistically significant (p=0.13). Oxybutynin also reduced HF intensity in the analyzed women, but it was not statistically significant (p=0.19) when compared to placebo. Although the calculated relative risk (RR) showed a protection from oxybutynin to HF intensity in these patients, it was also not statistically significant, being RR=0.65 and 95% confidence interval (CI) 0.78–1.98.

Table 3 shows the adverse effects reported by the patients of each arm. Interestingly, more women in placebo arm reported anticholinergic adverse effects such as xerostomia, headache, diarrhea, and dry skin. Even though only one woman reported tachycardia and decrease in appetite in the oxybutynin arm, there was no statistically significant difference between the two

Table 1. Baseline characteristics of the study population.

	Total (n=24)	Oxybutynin (n=12)	Placebo (n=12)	p-value
Mean age, y±SD (range)	51.5±5.50 (34–62)	51.8±3.46 (48–59)	51.2±7.15 (34–62)	**0.02**
Menstrual state (%)				
Premenopausal	2 (8.3)	0	2 (16.6)	0.48
Postmenopausal	22 (91.7)	12 (100)	10 (83.4)	
Ethnicity (%)				
White	15 (62.5)	7 (58.3)	8 (66.7)	0.99
Nonwhite	9 (37.5)	5 (41.7)	4 (33.3)	
TNM status				
T status (%)				
Tis	2 (8.3)	0	2 (16.6)	0.49
T1	9 (37.5)	5 (41.7)	4 (33.4)	
T2	10 (41.7)	5 (41.7)	5 (41.7)	
T3	3 (12.5)	2 (16.6)	1 (8.3)	
T4	0	0	0	
N status (%)				
N0	14 (58.3)	7 (58.3)	7 (58.3)	0.45
N1	6 (25.1)	2 (16.7)	4 (33.4)	
N2	2 (8.3)	2 (16.7)	0	
N3	2 (8.3)	1 (8.3)	1 (8.3)	
HF intensity (%)				
Mild	1 (4.2)	0	1 (8.3)	0.30
Moderate	8 (33.3)	6 (50.0)	2 (16.6)	
Severe	8 (33.3)	3 (25.0)	5 (41.7)	
Very severe	7 (29.2)	3 (25.0)	4 (33.4)	

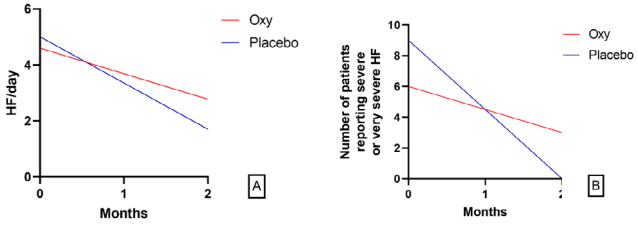
Nonwhite: black, brown, yellow, and indigenous ethnicity; TNM: tumor, node, and metastasis; HF: hot flashes.

groups in adverse effects (p=0.37), showing that oxybutynin was well tolerated at this dose.

Among patients that started the study, only one in the oxybutynin arm was excluded from the analyses since she stopped taking the medication, reporting having unbearable dizziness.

DISCUSSION

TAM is a well-established medication used for the treatment of ER+ BC, leading to a significant reduction in deaths when in the adjuvant setting, and reducing by 34.0% the incidence of ER+ BC in women at high risk of developing the disease[21,22]. This prodrug needs to undergo hepatic metabolism by CYP2D6 to activate its metabolites 4-hydroxytamoxifen and endoxifen, both with a much higher level of affinity for ER than TAM itself[15]. Elevated endoxifen plasma levels suggest that this metabolite is clinically more important in TAM efficacy than 4-hydroxytamoxifen[23]. However, the use of TAM can be associated with adverse effects such as HF in approximately 80.0% of patients[24]. Additionally, it is believed that the conversion of TAM to endoxifen is the cause of HF, and it is also assumed as a biomarker of efficacy[15].



HF: hot flashes; Oxy: oxybutynin.

Figure 2. Hot flashes scores (A) and intensity (B) reduction by oxybutynin and placebo.

Table 2. Reduction in hot flashes score and intensity from baseline to month 2.

HF measure	Oxy Baseline (n=12)	Oxy Month 2 (n=11)[a]	p*	Placebo Baseline (n=12)	Placebo Month 2 (n=12)	p†	Mean (SD) reduction Oxy (% of reduction)	Mean (SD) reductionPlacebo (% of reduction)	p††	RR (95%CI)
HF score (%)										
I	0	7 (63.6)		2 (16.7)	11 (91.7)		1.81±1.01 (60.3)	3.33±2.99 (33.4)	0.13	1.21 (0.78–1.98)
II	7 (58.3)	3 (27.3)		5 (41.6)	1 (8.3)					
III	4 (33.4)	0	>0.99	1 (8.3)	0	**0.04**				
IV	0	0		2 (16.7)	0					
V	1 (8.3)	1 (9.1)		2 (16.7)	0					
HF intensity (%)										
Mild	0	6 (54.5)		1 (8.3)	9 (75.0)		(54.5)	(83.3)	0.19	0.65 (0.87–5.56)
Moderate	6 (50.0)	2 (18.2)	0.40	2 (16.6)	3 (25.0)	**<0.01**				
Severe	3 (25.0)	2 (18.2)		5 (41.7)	0					
Very severe	3 (25.0)	1 (9.1)		4 (33.4)	0					

[a]One patient in the oxybutynin arm was excluded from this analysis since she stopped taking the medication because of reported dizziness.
HF: hot flashes; Oxy: oxybutynin 5 mg/day; HF score: I = 1 to 2 HF/day, II = 3 to 4 HF/day, III = 5 to 6 HF/day, IV = 7 to 8 HF/day, V = 9 to 10 HF/day; RR: relative risk; 95%CI: 95% confidence interval; p*: p-value from the difference between the reduction of HF score and HF intensity of oxybutynin 5 mg/day from baseline to month 2; p†: p-value from the difference between the reduction of HF score and HF intensity of placebo from baseline to month 2; p††: p-value from the difference between the reduction of HF score and HF intensity of oxybutynin 5 mg/day and placebo.

Table 3. Self-reported adverse effects from baseline to month 2.

Adverse effects	Oxy (%) (n=11)	Placebo (%) (n=12)	p-value	RR (95%CI)
Headaches	0	1 (8.3)	0.37	0.44 (0.64–5.56)
Xerostomia	0	2 (16.6)		
Diarrhea	0	1 (8.3)		
Dry skin	0	1 (8.3)		
Tachycardia	1 (9.1)	0		
Decrease in appetite	1 (9.1)	0		

Oxy: oxybutynin 5 mg/day; RR: relative risk; 95%CI: 95% confidence interval.

HF are the subjective and transitory sensation of heat, flushing, and excessive sweating in the face and chest, and it generally occurs as a result of decreased estrogen or increased gonadotropin concentrations[24-27]. Furthermore, other reported precipitators include psychological stress, hot weather, alcohol, and caffeine[28]. The physiological and molecular mechanism of HF is still unknown[29]; however, it is known to be triggered by a small elevation in core body temperature that induces activation of the sympathetic nervous system by peripheral vasodilation and increased activity of sweat glands. It is believed that this mechanism is associated with the response of the hypothalamus to decreased estrogen levels and the modulation of serotonin and noradrenalin[30]. Thus, HF can result in sleep disturbance, headache, irritability, and in reduced quality of life[31].

Pharmacologically, the most used medications are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), megestrol, clonidine, and gabapentin. However, there is a frequent association of these drugs with weight gain, and it is not frequent that patients become refractory to treatment, even after the most effective agents, like SSRIs[32]. Therefore, in the need of new medications to improve quality of life, oxybutynin emerges as a plausible drug since it is an anticholinergic agent that can interfere with the postjunctional effects of acetylcholine on smooth muscle, causing smooth muscle relaxation of the bladder and blood vessels[33,34]. Oxybutynin presents selectivity for the M3 and M1 muscarinic subtypes, which can be found in the brain, and this central effect may diminish the thermostat level and sweating threshold, reducing HF severity and frequency[32].

In this work, oxybutynin 5 mg/day was administered to BC women using TAM for two months (8 weeks). Although this concentration did not differ statistically from placebo, it was possible to see that it actually reduces the number and intensity of HF/day. These results partially corroborate Leon-Ferre et al.[18], who also investigated oxybutynin 5 mg/day and 10 mg/day versus placebo for HF reduction in women with or without BC, using TAM or not, and found that these two doses of oxybutynin were efficient in decreasing HF in those women. There were some differences in the methodology applied, such as the period the oxybutynin was administered. The authors administered the doses for six weeks, twice a day (2.5 mg twice a day and 5 mg twice a day), finding statistical difference between placebo and both doses. Simon et al.[35] also evaluated oxybutynin versus placebo, in the dose of 15 mg once a day, for 12 weeks in postmenopausal women, and found statistical difference in HF reduction in women treated with oxybutynin, besides the improvement in sleep quality, sleep disturbance, and the global sleep index.

In our study, women in the placebo arm reported more anticholinergic adverse effects than in the oxybutynin arm, although one patient discontinued the study since she felt severe dizziness. Adverse effects of anticholinergic drugs, such as xerostomia, constipation or diarrhea, decrease in appetite, dizziness, and dry eyes and skin are expected. But our study showed that a low dose of oxybutynin for a short period presented very tolerable adverse effects.

One important advantage of oxybutynin over SSRIs and SNRIs is that oxybutynin does not interfere with CYP2D6, since this enzyme is important for TAM metabolism. The use of this enzyme, and its consequent inhibition, can decrease endoxifen plasma levels; studies are still debating if this inhibition can interfere with TAM anticancer efficacy[36-39].

Although the sample size is adequate for a pilot study, the small cohort and short duration are limitations for the results. And although the dose needs to be adjusted, the short duration showed a preclusion of long-term safety of oxybutynin for BC patients in use of TAM. A new study with an expanded casuistic is going to be conducted with registration in the Brazilian Registry of Clinical Trials.

CONCLUSIONS

Oxybutynin is a safe nonhormonal therapy option for hot flashes in women with breast cancer in use of tamoxifen. More studies are needed to better adjust the dose and period of oxybutynin for higher efficacy.

AUTHORS' CONTRIBUTIONS

BFM: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. MGO: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. VTO: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. LEK: Formal analysis, Project administration, Supervision, Validation, Writing - review & editing. SUS: Conceptualization, Formal analysis, Validation, Writing - original draft. RSS: Conceptualization, Project administration, Supervision, Writing - review & editing.

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CASE REPORT
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Therapeutic approach to triple negative breast cancer in pregnant woman: case report

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ABSTRACT

Pregnancy-associated breast cancer includes tumors that occur during pregnancy, lactation, or within one year postpartum. It is a rare clinical condition, with an incidence ranging from 1:3,000 to 1:10,000 pregnancies. Therapeutic strategies take into account factors such as tumor staging, patient characteristics, and gestational age. Radical mastectomy was the main surgical intervention in triple-negative breast cancer. Currently, studies suggest that mastectomy should not be mandatory for the treatment of breast cancer solely due to the presence of pregnancy, and breast conservation is discussed whenever possible. Despite the aggressive biology of the triple-negative subtype, approximately 40% of patients have tumors that are highly sensitive to chemotherapy, achieving a complete pathological response. The objective of this study was to report a clinical case of breast cancer in a young pregnant patient, describing the clinical presentation, histological characteristics, as well as the diagnostic methods and therapeutic measures adopted, with the aim of contributing didactically to the academic community, offering theoretical support for the improvement of clinical practice in the management of triple-negative breast cancer during and after the gestational period.

KEYWORDS: therapeutic approach; triple negative breast cancer; pregnant.

INTRODUCTION

Breast cancer is a heterogeneous disease with great variation in its morphological and molecular characteristics and in its clinical response. Worldwide, it is the most common cancer in women, being a frequent cause of cancer death in this population, with an estimated 660,000 deaths for the year 2024[1]. Pregnancy-associated breast cancer, by definition, includes tumors that develop during pregnancy, lactation or within one year of the postpartum period. However, some studies suggest extending this concept to up to 5 - 10 years postpartum given the clinical implications of this period in recurrence and mortality from breast cancer[2]. Its incidence ranges from 1:3,000 to 1:10,000 pregnancies, being a rare clinical condition, although there is a tendency for it to grow, since women have been delaying motherhood[3,4].

It is known that pregnancy and lactation promote the creation of a microenvironment with high carcinogenic potential in the breast through remodeling of the glandular architecture and high hormone concentration, which thus favors tumor proliferation[5,6]. Despite this, the majority of breast cancers associated with pregnancy are not hormone-dependent, with triple negative being the most prevalent subtype in this population[5].

Diagnosis is a clinical challenge as there is a transposition of signs and symptoms resulting from physiological changes during pregnancy, such as increased breast density and volume, with the repercussions of neoplasia, in addition to restrictions on the use of imaging tests. This makes screening and early detection of the problem difficult[2,5].

The therapeutic approach should be multidisciplinary, defining the modality and sequence of treatment depending on the characteristics related to the tumor and the gestational age, as well as the patient's preferences[2]. For decades, radical mastectomy was the main surgical intervention for triple-negative breast cancer. However, this procedure implies numerous repercussions in the patient's life, such as the development of lymphedema and other postoperative complications, decreased self-esteem, impact on femininity and sexuality, and the development of psycho-emotional disorders[7].

Currently, there are promising methods of organ preservation and prosthesis surgery, the feasibility and efficacy of which are being discussed[8]. Furthermore, despite the aggressive biology of the triple-negative subtype, approximately 40% of patients have tumors that are highly sensitive to chemotherapy, achieving a complete pathological response[9]. However, because it is

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a relatively rare indication, therapeutic approaches are mostly derived from large trials in non-pregnant women. Thus, evidence that takes into account the repercussions on the mother-fetus binomial remains scarce or controversial[10].

The objective of this study was to report a clinical case of breast cancer in a young pregnant patient, discussing the clinical presentation, histological characteristics, as well as the diagnostic methods and therapeutic measures adopted. The aim was to contribute didactically to the academic community, offering theoretical support for the improvement of clinical practice in the management of triple-negative breast cancer during the gestational period.

CASE REPORT

This study was approved by the institution's ethics committee under the Certificate of Presentation for Ethical Appreciation (CAAE): 80536624.5.0000.5176.

A 26-year-old female patient, GIIIPIIA0, in the second trimester of pregnancy, was treated at a hospital in the state of Paraíba, Brazil, in November 2022, complaining of a lump in her left breast for six months. After core needle biopsy and immunohistochemistry analysis, the patient was diagnosed with infiltrating ductal carcinoma in the left breast, with negativity for estrogen and progesterone receptors, negative HER2 and KI67 of 70%. At 24 weeks of gestational age, she started a chemotherapy regimen with cyclophosphamide and doxorubicin, in four cycles, with intervals of 21 days. The doses varied between 951.51 and 1141.95 mg for cyclophosphamide and 95.15 mg and 114.19 mg for doxorubicin, with the treatment being suspended two weeks before delivery.

In April 2023, she returned for evaluation, when a breast ultrasound (USG) was requested, which revealed a nodular image with BI-RADS 6 in the left breast, markedly hypoechoic, with irregular contours, with discrete, punctiform and peripheral vascularization on Doppler, heterogeneous content and a combined pattern of posterior acoustic reinforcement, measuring 4.53 x 3.35 cm and 2.18 cm from the skin to the center of the nodule and extending to the subdermal region (Figure 1). The right breast showed no changes. In addition, the retromammary fascia had preserved integrity and the armpits were without abnormalities in both breasts. In that same month, at 38 weeks of gestational age, the patient underwent cesarean section, which occurred uneventfully, with the birth of a male neonate, with good vitality. Breastfeeding was not recommended from the first postpartum moment.

Three weeks after the cesarean section, a new neoadjuvant treatment plan was started with a weekly regimen of carboplatin and paclitaxel, in 12 sessions. In the first eight sessions, carboplatin 285 mg and paclitaxel 144 mg were used. The patient developed nephrotic colic, and the dose of the four subsequent sessions was reduced by 20%. In a new radiological evaluation in September 2023, dimensions of the lesion became 1.78 cm (in its largest diameter) and 1.77 cm from the skin, maintaining the characteristics of the previous ultrasound examination. The following month, a quadrantectomy was performed with evaluation of the sentinel lymph node, which concluded that it was free of neoplasia. The material received for histopathological study included a left breast segment measuring 12.0 x 8.5 x 5.0 cm, with a white-yellowish nodular tumor lesion measuring 2.5 x 1.7 cm, which was classified as grade III invasive ductal carcinoma, with free surgical margins.

In November 2023, she began adjuvant chemotherapy with capecitabine for eight cycles. Three months later, the patient returned for consultation reporting nodules in the operated breast, and a new ultrasound was requested, which showed local recurrence with the presence of 1.04 cm nodules in the union of the upper quadrants and 1.2 cm in the upper lateral quadrant of the left breast. In April 2024, the patient began adjuvant radiotherapy. She then returned for preoperative evaluation, and a left breast mastectomy with immediate prosthesis reconstruction was proposed, which was then performed in June 2024. The surgical specimen was sent for histopathological study. The material received for examination contained a product weighing 710 g and measuring 18 x 16 x 5.0 cm. The sections revealed two irregular, yellowish-white, firm-elastic areas measuring 0.9 x 0.8 and 0.4 x 0.3 cm, 4.0 and 3.5 cm from the deep margin, respectively, and 1.2 cm apart. The analysis showed residual invasive ductal carcinoma, with neoplasia present in two of eight slides, with the largest focus measuring 0.8 cm.

In September 2024, the patient began adjuvant chemotherapy with a combination of carboplatin and docetaxel, in six sessions, with a 21-day interval. In the first session, she used carboplatin 960 mg and docetaxel 138 mg. In subsequent sessions, there was an 80% reduction in the dose due to the patient's fever, myalgia and fatigue after the first cycle. She is currently undergoing chemotherapy treatment, with a cranial tomography, abdominal MRI and chest X-ray showing no evidence of metastasis.

DISCUSSION

In this article, we present the case of a patient diagnosed with triple-negative breast cancer detected during pregnancy, whose course presented clinical challenges that interfered with the antineoplastic approach.

Triple-negative breast cancer is defined by no or minimal staining for estrogen and progesterone receptors and lack of overexpression of human epidermal growth factor receptor 2 (HER 2), which is associated with a higher risk of recurrence and worse overall prognosis[8]. This subtype is associated with aggressive behavior and is more common in pregnant patients than in non-pregnant patients. Therefore, therapeutic strategies should take into account factors such as tumor staging, patient characteristics, and gestational age[2].

For patients in the first trimester, treatment options are limited during the first weeks of pregnancy, since endocrine treatments are not viable and chemotherapy is prohibited during

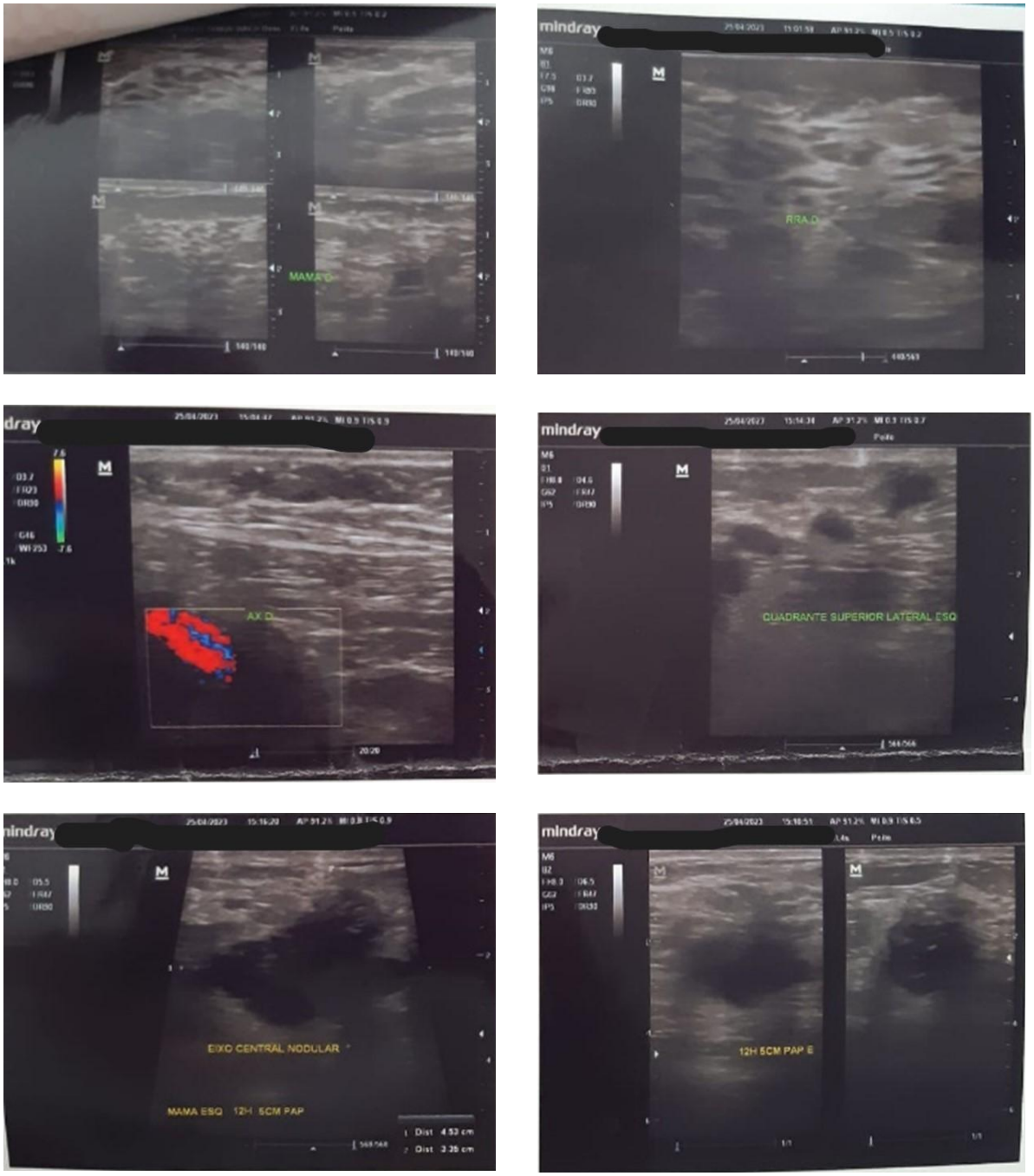

Figure 1. Breast ultrasound revealing a nodular image with BI-RADS 6 in the left breast, markedly hypoechoic, with irregular contours, with discrete, punctiform and peripheral vascularization on Doppler, with heterogeneous content and a combined pattern of posterior acoustic enhancement, measuring 4.53 x 3.35 cm.

this period due to teratogenicity. Surgical treatment, in turn, is considered safe at any time during pregnancy[11]. In patients diagnosed with breast cancer in the second or third trimester, as in the case described, conservative therapeutic modalities are recommended, as is the case for most non-pregnant patients[2].

Regarding systemic therapy, chemotherapy can be neoadjuvant or adjuvant, depending on the overall treatment plan[2]. The greatest experience with chemotherapy for breast cancer during pregnancy comes from regimens that use various combinations of doxorubicin, cyclophosphamide and fluorouracil[11]. The taxanes, such as paclitaxel and docetaxel used in this case, are a group of antineoplastic drugs with antimitotic action that appear to improve the prognosis of women with breast cancer, especially those with lymph node involvement. However, there is limited data on their use during pregnancy[12].

Furthermore, the inclusion of platinum agents, such as carboplatin, as neoadjuvant chemotherapy for triple-negative breast

cancer remains controversial because, despite the improvement in pathological complete response, the long-term results remain unknown[13]. Capecitabine and olaparib, as adjuvant therapy, have shown an improvement in the prognosis of patients with residual HER2-negative invasive breast cancer after neoadjuvant chemotherapy[14]. It is worth noting that chemotherapy should be suspended at least three weeks before delivery to allow a window for maternal and fetal bone marrow recovery between chemotherapy cycles, thus avoiding hematologic complications during delivery[3,15].

Regarding the surgical approach, it can be performed safely during any stage of pregnancy[16]. The timing of the procedure should be determined based on the gestational age, the characteristics of the patient and the tumor. However, it is worth noting that in cases of elective surgery, it is preferable to postpone it until after delivery[2]. For decades, mastectomy was considered the standard treatment for patients with breast cancer during pregnancy[17]. However, studies suggest that mastectomy should not be mandatory for the treatment of breast cancer simply because of the presence of pregnancy, and that breast conservation should be discussed whenever possible[16]. Therefore, as in non-pregnant patients, the ideal choice of procedure is based on a shared decision made by the patient and the physician after discussing the risks and benefits between mastectomy and conservative surgery in relation to long-term survival, the risk of local recurrence and the impact on the aesthetic result and overall quality of life[11,17].

In the perioperative context, sentinel lymph node testing is the standard procedure for axillary evaluation in patients with early-stage breast cancer and negative clinical examination, thus helping to define the need for axillary lymphadenectomy[18]. However, during the gestational period, adherence to this procedure is still not a consensus in the literature, and there is not enough data to make basic recommendations for its use in this scenario, making it necessary to individualize the cases of indication[11].

Regarding radiotherapy, it is rarely indicated in pregnant women with breast cancer, since fetal tissues are sensitive to radiation, and the risks of toxicity depend on gestational age[10]. In general, it is indicated in patients who opt for breast conservation or who require post-mastectomy radiation. The start of treatment is essential, since patients undergoing surgery with adjuvant radiation should start radiotherapy within 8 to 12 weeks to maintain disease-free survival and avoid an increased risk of local recurrence[17].

Breast reconstruction after mastectomy is a critical element in the treatment of breast cancer, especially at a young age. The literature demonstrates the reduction of the emotional impact of the injury in immediate reconstruction[4]. However, in order to reduce the time of anesthesia and complications of surgery, delayed reconstruction is preferable[19]. Therefore, an individualized and multidisciplinary strategy is key in the treatment of these women[4].

It is known that termination of pregnancy does not change the prognosis and that induced abortion in this situation is not permitted by Brazilian law. Therefore, patients must be monitored in a high-risk obstetrics unit, and the timing of delivery must take fetal maturation into account[3]. Thus, the preferred route of delivery is vaginal if there are no contraindications, and oncological treatment can be resumed immediately after delivery. That said, it is extremely important that the patient receives obstetric, oncological, pediatric, radiotherapy, ethical and psychological guidance during treatment, since this has a significant impact on pregnancy, postpartum, breastfeeding and even the woman's reproductive life[2].

Therefore, a multidisciplinary approach to these patients is essential to ensure good care and maternal and fetal well-being. As with non-pregnant patients, every effort should be made to provide the patient with maximum benefit and the best prognosis in the gestational context[20].

CONCLUSIONS

This report highlights the complexity and therapeutic challenges involved in the management of triple-negative breast cancer in a pregnant patient, emphasizing the importance of a multidisciplinary approach. Given that the incidence of breast cancer during pregnancy is rare, it is essential to develop more reports and studies documenting similar cases, with the aim of improving treatment guidelines and offering better therapeutic options for these cases.

AUTHORS' CONTRIBUTION

TPS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. VRL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. ATU: Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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REVIEW ARTICLE
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Vacuum-assisted biopsy and excision of breast lesions: review and current indications

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ABSTRACT

Vacuum-assisted biopsy is an advance in breast diagnostics because it is a less invasive and more practical approach than conventional surgery, capable of diagnosing and treating certain lesions. Despite the still limited availability of the method, related to its cost and the number of professionals qualified to perform it, the potential of vacuum-assisted biopsy and excision in the practice of mastologists is unquestionable. The attending physician is expected to understand the methods, as well as the indications pertinent to them. Recognizing the impossibility of exhausting the subject, the objective of this study is to conduct a narrative review, summarizing the indications for vacuum-assisted breast biopsy and excision currently, according to the available scientific evidence.

KEYWORDS: biopsy; large-core needle; image-guided biopsy.

INTRODUCTION

The evolution of breast biopsy techniques began in 1960, with the advent of fine-needle aspiration biopsy (FNA), widely used until the 1990s, enabling cytopathological analysis of the lesion and the possible distinction between malignancy and benignity. Incorporated into the routine diagnosis of breast lesions, together with clinical evaluation and imaging examination, FNAB had a non-diagnosis rate of 40%[1]. Given the diagnostic limitations of the method, a new puncture technology was developed: core needle biopsy, also known as core biopsy. This new technique consists of an automatic device, with a large-caliber needle, capable of biopsying an entire fragment of the lesion and thus providing histological study, providing greater detail on benignity or malignancy, as well as the diagnosis of ***in situ*** or invasive lesions. In the mid-1990s, core biopsy became the standard intervention for diagnosing breast lesions with superiority based on a successful biopsy rate of 99% of cases, compared to 60-75% for FNA[2], and a sensitivity of 80-93%, compared to 65-82% for FNA[3].

Approved by the Food and Drug Administration (FDA) in April 1995, vacuum-assisted biopsy, also known by the abbreviation VAB, has been used in medical practice in Brazil ever since, and has been progressively incorporated into the list of mandatory minimum coverage for health insurance plans in the country by the National Supplementary Health Agency (ANS). With the latest update in February 2021, ANS began granting access to VAB via ultrasound, stereotactics and magnetic resonance imaging in certain clinical contexts[4,5].

VAB is a safe, fast and effective technique for excising breast fragments, whose equipment basically consists of a biopsy needle coupled to a rotational cutter, a suction chamber and a device capable of creating a vacuum. The procedure is performed through a single incision in the skin, with the biopsy needle being inserted only once, since the material collected in each cycle is collected by suction into the reservoir chamber[6]. The effectiveness of VAB is based on its greater technical precision and broader sampling compared to core biopsy, since VAB needles range from 8G to 14G, with the capacity to collect between 40 mg and 300 mg of tissue per fragment, while core biopsy has an average collection of 17 mg of tissue per fragment[7].

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Explored in the context of breast biopsy for years, VAB has become a consolidated and improved technique, which culminated in the idea of also making it an option for therapeutic proposal for some types of breast lesions. With the approval of the FDA in 2002, vacuum-assisted excision, recognized by the abbreviation VAE, proposes the complete excision of breast lesions using needles larger in diameter than those used in VAB, but maintaining its outpatient nature, under local anesthesia to avoid surgical excision, whose complexity and costs are significantly greater[6,7].

METHODS

This study aimed to address the topic of vacuum-assisted biopsy and excision of breast lesions, with an emphasis on current indications for the procedure. The search was conducted in the PubMed, Medline, Embase, and Cochrane databases, using the following search terms: "Biopsy", "Large-Core Needle", and "Image-guided biopsy". Articles published between 2006 and 2023, in English and Portuguese that directly addressed breast biopsy and vacuum-assisted excision of breast lesions were included. The period from 2006 to 2023 was chosen to cover the development and consolidation of the techniques, considering from the approval of vacuum-assisted excision by the Food and Drug Administration (FDA) in 2002 to the most recent studies available. The inclusion criteria considered original articles, reviews, clinical practice guidelines, and relevant studies related to the topic. Duplicate publications, articles that dealt with techniques unrelated to the topic, and those unavailable in full text were excluded. The articles identified in the search were screened in two stages: initially, through the analysis of titles and abstracts; then, by reading them in full to determine if the inclusion criteria were met. After applying the inclusion and exclusion criteria, 20 articles were selected for analysis, considering their relevance and alignment with the objective of this study. In addition to the articles, the normative resolutions of the National Supplementary Health Agency (ANS) were analyzed, especially with regard to the coverage of procedures by supplementary health in Brazil, to complement the analysis on clinical applicability. Because this is a narrative review, the absence of systematic criteria and the subjective choice of articles may limit the reproducibility of the study and introduce biases. However, efforts were made to ensure the inclusion of relevant and updated publications, with the aim of providing a comprehensive and informative view on the topic.

RESULTS AND DISCUSSION

Core needle biopsy vs. vacuum-assisted biopsy

Core needle biopsy is the routine diagnostic method because it provides a quality diagnosis, is easy to perform, is minimally invasive and has a lower cost than surgical excision. In this scenario, both core biopsy and vacuum-assisted aspiration are feasible options, although the clinical decision to choose one or the other is sometimes not simple and carries doubts about the possibility of false negatives and diagnostic underestimation[8,9]. Compared to core biopsy, vacuum-assisted biopsy offers larger samples, lower false negative rates, lower rebiopsy rates and lower diagnostic underestimation[7,10]. In this scenario, the indications for vacuum-assisted aspiration have grown and have been reaffirmed by studies and positive statistical numbers.

Regarding concerns about false-negative results and diagnostic underestimation, the diagnostic upgrade rate is the parameter for comparison between methods. The upgrade rate is defined by the presence of malignancy after surgical excision of the lesion previously biopsied or during its clinical-imaging follow-up[11].

Regarding the use of VAB in the diagnostic investigation of breast lesions with malignant potential, comparative studies show that, in cases of atypical ductal hyperplasia, the diagnostic upgrade rate for ductal carcinoma ***in situ*** was reduced from 50% to 20%; but in cases of ductal carcinoma ***in situ,*** the diagnostic upgrade rate for invasive ductal carcinoma was 30% to 10%, when comparing the results of core biopsy and VAB, respectively[12].

Other studies analyzing the upgrade rate in VAB show variable trends towards malignancy in specimen analysis or in clinical follow-up. A retrospective study showed an upgrade rate of 0.4% and a confidence interval between 0.1% and 2.1% when analyzing lesions of uncertain behavior without atypia, while the upgrade rate for lesions of uncertain behavior with atypia, such as flat epithelial atypia, atypical ductal or lobular hyperplasia, and lobular carcinoma ***in situ***, was 4.7% with a confidence interval between 2.9% and 7.5%. The same study showed that the upgrade rate is significantly increased when two or more lesions coexist in the same biopsied area[11].

VAB has a higher cost per biopsy needle when compared to core biopsy needle; therefore, for lesions in which VAB is not the first method of choice, cost-effectiveness should be taken into consideration and core biopsy should be considered. On the other hand, in lesions for which VAB is used, the higher cost of the needle is outweighed by the benefits of diagnostic accuracy. Grady et al.[13] refers to a study conducted in 2015 reviewing data from the American Society of Breast Surgeons between 2001 and 2014, containing data from 31,451 patients, in which information on biopsy, rebiopsy, instrument used to perform the biopsy and the cost per breast cancer diagnosis in each situation were evaluated, using a linear mathematical model. The study resulted in an average cost per case diagnosed by core biopsy of $4,346 (4,327–4,366) and of $3,742 (3,732–3,752) to $4,779 (4,750–4,809) per VAB, with variation related to the brand of the device used. The study concluded that VAB would be more cost-effective, provided that the best-performing devices were chosen.

Vacuum-assisted biopsy vs. Vacuum-assisted excision

In addition to its investigative role, VAB also has an established therapeutic role. Unlike vacuum biopsy, which has a purely diagnostic purpose and does not require complete removal of the lesion, VAE aims to replace diagnostic surgical biopsy by removing the lesion in its entirety. The VAE technique stipulates that the aspiration be orthogonal, rather than oblique, to the lesion, and it also stipulates complete removal of the lesion and its periphery to ensure greater diagnostic accuracy[14]. To perform VAE, the needles used are larger in size, ranging from 7G to 10G, with the capacity to obtain large and varied amounts of tissue. There is no consensus on the size of the lesion to be approached, and according to Park et al.[15], there is no limit to the size to be excised, which should be guided by the characteristics of the lesion, its location and the patient's particularities. At the end of the procedure, radiological verification showing the absence of the target lesion is mandatory, as well as subsequent assessment of imaging and histopathological compatibility.

Vacuum-assisted excision vs. conventional surgical approach

VAE is a subject of broad debate due to the high variability in the rates of upgrade to malignancy of lesions treated with the technique. The defense of vacuum excision with subsequent clinical follow-up is based on the personalization of treatment and advocates the de-escalation of invasive procedures associated with strategies to not underestimate the patient's subsequent specific risk of developing breast cancer, while opposition to vacuum aspiration points to the lack of standardized protocols and robust evidence as factors that prevent the widespread use of the method[11]. Based on the BI-RADS (Breast Imaging Reporting and Data System) classification system, an upper safety limit can be inferred to be an underestimation rate of up to 2% after vacuum-assisted aspiration procedures, which would be equivalent to a lesion classified as BI-RADS 3, in terms of probability of malignancy. Therefore, breast lesions with upgrade rates ≤2% after the procedure – a group generally composed of lesions without atypia – would be eligible for clinical follow-up in to avoid surgical approaches subsequent to biopsy.

In cases of lesions with atypia, carcinomas *in situ*, invasive carcinomas and lesions with clinical-radiological-histopathological discordance, conventional surgery is mandatory in the therapeutic management, since vacuum aspiration violates the basic principle of oncological surgery, which is the ability to perform a single-block excision of the lesion, in addition to the possibility of evaluating the margins of the specimen, which must be free of neoplasia[8]. However, there are studies aimed at proving the role of excision by vacuum aspiration even in these scenarios.

Valadares et al.[16] published in 2023 a retrospective study evaluating data from 116 patients who underwent vacuum aspiration of BI-RADS 4, BI-RADS 5 breast lesions or lesions with a diagnosis of uncertain malignant potential (B3) in a previous core biopsy, with anatomopathological results of *in situ* or invasive breast carcinoma of the aspirated specimens. These patients subsequently underwent conventional surgery to evaluate the existence of residual disease, and the result of the study was promising, mainly for low or moderate grade pT1a and pT1b tumors, which provides data to support the selection of criteria for future prospective trials on the subject. Regarding data on cost and effectiveness, Whitworth et al.[17] conducted a retrospective cohort study, analyzing the amounts spent on the treatment of benign lesions and high-risk lesions treated by vacuum aspiration compared to similar lesions treated surgically. The study showed that VAE, in both the scenario of benign lesions and in the scenario of high-risk lesions, has a cost approximately 60% lower than the surgical approach, without compromising the quality of treatment.

Indications for vacuum-assisted biopsy

VAB has proven to be an accurate technique for treating suspicious breast calcifications, as shown in Figure 1, significantly reducing the need for rebiopsy (8), since this is a small breast alteration that can be seen primarily only on mammography, making core biopsy even more technically difficult and with less favorable success rates. The same logic applies to tiny, non-palpable lesions and intracystic lesions, for which core biopsy needle shots are less likely to be accurate in relation to the lesion and, therefore, have lower diagnostic sensitivity, making VAB the best option in this scenario[1,5,6]. With advances in imaging in the context of the breast, magnetic resonance imaging has become an important imaging method for detecting lesions suspected of malignancy. With an emphasis on lesions seen only by this method, areas of nodular or non-nodular enhancement, with no corresponding second-look ultrasound directed at such areas, have become lesions with indication for magnetic resonance-guided VAB[18]. Finally, some individual details of the cases make VAB

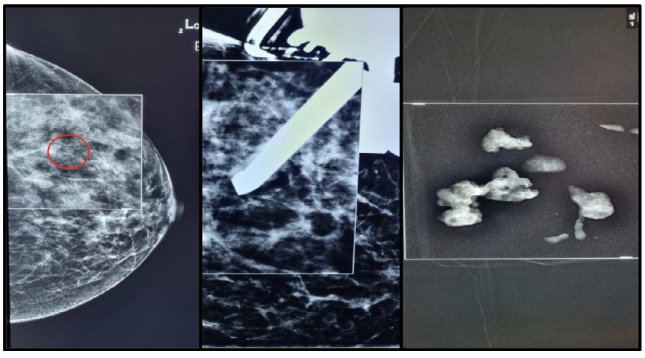

Figure 1. (A) Suspicious calcifications seen on mammography (red rim); (B) Image showing biopsy needle positioned below lesion; (C) Mammography image of biopsied tissue containing calcifications.

the method of choice, since, as it does not require triggering or advancement, it is safer when investigating nodules close to the chest, close to the skin, the nipple or implants[6].

Indications for vacuum-assisted excision

Regarding nodules that show growth, such as phyllodes tumor, studies demonstrate that VAE has a recurrence rate of 5% to 17% when evaluating lesions up to 3.3 cm, with lower recurrence rates in lesions less than 1.5 cm, which makes the procedure an alternative to surgery for benign tumors[19]. The method can be used to treat fibroadenoma, the most common benign breast tumor, with good results[10,12], and is also a potential treatment option for minor gynecomastia, for which there is no need for surgical reduction of the skin or the nipple-areola complex[20]. The indication for excision by vacuum aspiration extends to other breast lesions, such as radial scar and flat epithelial atypia, as long as they do not present atypia[14]. VAE is still the treatment used for intraductal papillary lesions, as show in Figure 2, with studies showing resolution in 97% of cases, in addition to preserving the viability of the function and sensitivity of the nipple-areola complex, which is often compromised after a conventional surgical approach[8]. However, it is important to emphasize that surgery is still the rule in cases of lesions with atypia, carcinomas in situ and lesions with clinical-radiological-histopathological discordance.

Complications

The possible complications of core biopsy and VAB are similar and are represented by hematoma, pain, infection, pneumothorax and skin injury. Hematoma is the main complication after vacuum-assisted aspirations, and small-volume hematomas do not require treatment. Surgery is necessary for hemostasis or debridement if there is suspicion of active bleeding or large-volume hematoma causing severe pain or secondary infection[5,10]. A 2019 retrospective study[21], including 4,776 patients undergoing VAB, identified complication in 6.7% biopsy cases. Of these, 96.2% were mild complications, which included hematoma that did not require treatment, mild pain, nausea, dizziness and itching or skin irritation, while only 3.8% were moderate complications, which included hematoma or bleeding requiring compressive treatment, vasovagal reaction or observation in the emergency room. Finally, in this study, no patient displayed serious complications, which would include post-biopsy infection, hematoma or bleeding requiring surgical treatment and death, arguing in favor of the safety of the method.

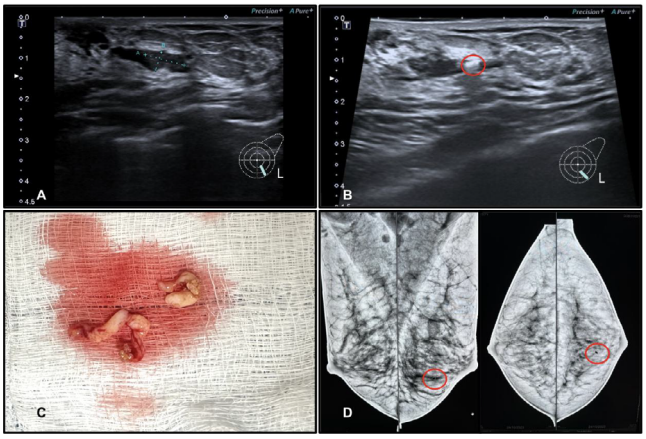

Figure 2. (A) Mixed intraductal lesion on USG; (B) Metal clip inserted after the procedure at the biopsy site (red rim); (C) Macroscopic image of the biopsied tissue; (D) Mammography image after the procedure with confirmation of clip at the biopsy site.

CONCLUSIONS

Vacuum-assisted aspiration has proven to be a highly valuable and potential procedure. Approved by the ANS in 2021, it is mandatory for health insurance plans to provide histopathological studies of non-palpable lesions, breast microcalcifications, intraductal or intracystic lesions suspected of being papillomas, nodular or non-nodular enhancements seen on magnetic resonance imaging, categorized as 4 or 5 in the BI-RADS classification, or in cases of nodules smaller than 2 cm, also categorized as 4 or 5 in the BI-RADS classification, in scenarios where doubts remain after core biopsy[4]. It is a comprehensive diagnostic and therapeutic method that because of its minimally invasive nature and association with high efficacy tends to contribute greatly to mastology[5,10,11]. Future studies will be essential to guide, on the basis of robust evidence, protocols that optimize the application of the technique for each type of breast lesion, ensuring greater precision and clinical benefit.

AUTHORS' CONTRIBUTION

LMACL: Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. GRA: Data curation, Formal Analysis, Supervision, Validation, Writing – review & editing. TPM: Data curation, Formal Analysis, Supervision, Validation, Writing – review & editing. JLCJ: Formal Analysis, Supervision, Validation, Writing – review & editing. EASA: Formal Analysis, Supervision, Validation, Writing – review & editing. RCSF: Formal Analysis, Supervision, Validation, Writing – review & editing. ADS: Formal Analysis, Supervision, Validation, Writing – review & editing. WJAJ: Formal Analysis, Supervision, Validation, Writing – review & editing. FMOC: Formal Analysis, Supervision, Validation, Writing – review & editing. JTCA: Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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